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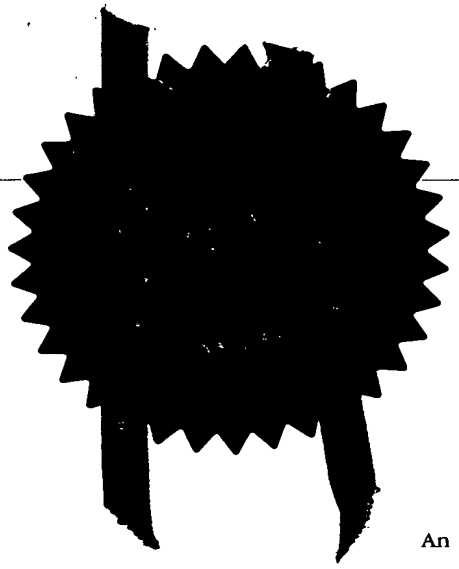

Signed R. Mahoney

Dated 28 July 1999

Patent Form 1/77

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3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

KARO BIO AB

Novum S-141 57
Huddinge
SWEDEN

Patents ADP number *(if you know it)*

6477871002

If the applicant is a corporate body, give the country/state of its incorporation

Sweden

4. Title of the invention

NOVEL THYROID RECEPTOR LIGANDS AND METHOD II

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

WITHERS & ROGERS
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Patents ADP number *(if you know it)*

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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Number of earlier application	Date of filing *(day / month / year)*

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b) there is an inventor who is not named as an applicant, or
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D.G. Bannerman
(01926) 336111

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NOVEL THYROID RECEPTOR LIGANDS AND METHOD II

Field of the Invention

This invention relates to novel compounds which are thyroid receptor ligands, and are preferably selective for the thyroid hormone receptor β, to methods of preparing such compounds and to methods for using such compounds such as in the regulation of metabolism.

Background of the Invention

While the extensive role of thyroid hormones in regulating metabolism in humans is well recognized, the discovery and development of new specific drugs for improving the treatment of hyperthyroidism and hypothyroidism has been slow. This has also limited the development of thyroid hormone agonists and antagonists for treatment of other important clinical indications, such as hypercholesterolemia, obesity and cardiac arrhythmias.

Thyroid hormones affect the metabolism of virtually every cell of the body. At normal levels, these hormones maintain body weight, the metabolic rate, body temperature, and mood, and influence serum low density lipoprotein (LDL) levels. Thus, in hypothyroidism there is weight gain, high levels of LDL cholesterol, and depression. In excess with hyperthyroidism, these hormones lead to weight loss, hypermetabolism, lowering of serum LDL levels, cardiac arrhythmias, heart failure, muscle weakness, bone loss in postmenopausal women, and anxiety.

Thyroid hormones are currently used primarily as replacement therapy for patients with hypothyroidism. Therapy with L-thyroxine returns metabolic functions to normal and can easily be monitored with routine serum measurements of levels of thyroid-stimulating hormone (TSH), thyroxine (3,5,3',5'-tetraiodo-L-thyronine, or T) and triiodothyronine (3,5,3'-triiodo-L-thyronine, or T). However, replacement therapy, particularly in older individuals is limited by certain of the deleterious effects of thyroid hormones.

In addition, some effects of thyroid hormones may be therapeutically useful in non-thyroid disorders if adverse effects can be minimized or eliminated. These potentially useful influences include weight reduction, lowering of serum LDL levels, amelioration of depression and stimulation of bone formation. Prior attempts to utilize thyroid hormones pharmacologically to treat these disorders have been limited by manifestations of hyperthyroidism, and in particular by cardiovascular toxicity.

Development of specific and selective thyroid hormone receptor agonists could lead to specific therapies for these common disorders while avoiding the cardiovascular and other toxicities of native thyroid hormones. Tissue-selective thyroid hormone agonists may be obtained by selective tissue uptake or extrusion, topical or local delivery, targeting to cells through other ligands attached to the agonist and targeting receptor subtypes. Thyroid

hormone receptor agonists that interact selectively with the β-form of the thyroid hormone receptor offers an especially attractive method for avoiding cardio-toxicity.

Thyroid hormone receptors (TRs) are, like other nuclear receptors, single polypeptide chains. The various receptor forms appear to be products of two different genes α and β. Further isoform differences are due to the fact that differential RNA processing results in at least two isoforms from each gene. The $TR\alpha_1$, $TR\beta_1$ and $TR\beta_2$ isoforms bind thyroid hormone and act as ligand-regulated transcription factors. In adults, the $TR\beta_1$ isoform is the most prevalent form in most tissues, especially in the liver and muscle. The $TR\alpha_2$ isoform is prevalent in the pituitary and other parts of the central nervous system, does not bind thyroid hormones, and acts in many contexts as a transcriptional repressor. The $TR\alpha_1$ isoform is also widely distributed, although its levels are generally lower than those of the $TR\beta_1$ isoform. This isoform may be especially important for development. Whereas many mutations in the TRβ gene have been found and lead to the syndrome of generalized resistance to thyroid hormone, mutations leading to impaired TRα function have not been found.

A growing body of data suggest that many or most effects of thyroid hormones on the heart, and in particular on the heart rate and rhythm, are mediated through the a-form of the TRa1 isoform, whereas most actions of the hormone such as on the liver, muscle and other tissues are mediated more through the β-forms of the receptor. Thus, a TRβ-selective agonist might not elicit the cardiac rhythm and rate influences of the hormones but would elicit many other actions of the hormones. It is believed that the α-form of the receptor is the major drive to heart rate for the following reasons:

1) tachycardia is very common in the syndrome of generalized resistance to thyroid hormone in which there are defective TRβ-forms, and high circulating levels of T_4 and T_3;

2) there was a tachycardia in the only described patient with a double deletion of the TRβ gene (Takeda et al, J. Clin. Endrocrinol. & Metab. 1992, Vol. 74, p. 49);

3) a double knockout TRα gene (but not β-gene) in the mouse has a slower pulse than control mice; and,

4) western blot analysis of human myocardial TRs show presence of the $TR\alpha_1$, $TR\alpha_2$ and $TR\beta_2$ proteins, but not $TR\beta_1$.

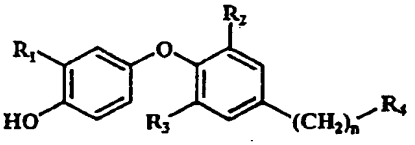
If these indications are correct, then a TRβ-selective agonist could be used to mimic a number of thyroid hormone actions, while having a lesser effect on the heart. Such a compound may be used for: (1) replacement therapy in elderly subjects with hypothyroidism who are at risk for cardiovascular complications; (2) replacement therapy in elderly subjects with subclinical hypothyroidism who are at risk for cardiovascular complications; (3) obesity; (4) hypercholesterolemia due to

elevations of plasma LDL levels; (5) depression; and, (6) osteoporosis in combination with a bone resorption inhibitor.

Description of the Invention

In accordance with the present invention, compounds are provided which are thyroid receptor ligands, and have the general formula I:

I



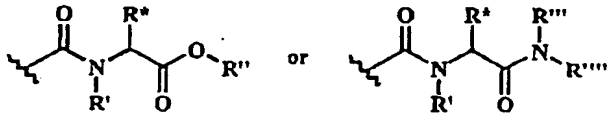
in which:

n is an integer from 0 to 4;

R_1 is alkyl of 1 to 6 carbons or cycloalkyl of 3 to 7 carbons;

R_2 and R_3 are the same or different and are hydrogen, halogen, alkyl of 1 to 4 carbons or cycloalkyl of 3 to 5 carbons, at least one of R_2 and R_3 being other than hydrogen;

R_4 is a heteroaromatic moiety which may be substituted or unsubstituted and is linked to $(CH_2)_n$ via a nitrogen atom or is a tetrazole moiety linked to $(CH_2)_n$ either via N or C, an amine (NR'R''), including those in which the amine is derived from an alpha amino acid of either natural (L) or unnatural (D) stereochemistry, a carboxylic acid amide (CONR'R'') or an acylsulphonamide ($CONHSO_2R'$) derivative, or a pharmaceuticallly acceptable salt thereof, and all stereoisomers thereof. The amine portion of the amide can be derived from a L or D alpha amino acid such as the general structure -CONR'R'' which can be represented by



and R', R'', R''' and R'''' are the same or different and are independently selected from hydrogen, alkyl, aryl and heteroaryl, substituted or unsubstituted, and R* may be hydrogen, alkyl, aryl and heteroaryl, substituted or unsubstituted, and may also be any of the side chains found in the naturally occuring alpha-amino acids.

In addition, in accordance with the present invention, a method for preventing, inhibiting or treating a disease associated with metabolism dysfunction or which is dependent upon the expression of a T_3 regulated gene is provided, wherein a compound of formula I is administered in a therapeutically effective amount. The compound of formula I is preferably an agonist that is preferably selective for the thyroid hormone receptor-beta. Examples of such diseases associated with metabolism dysfunction or are dependent upon the expression

of a T_3 regulated gene are set out hereinafter and include obesity, hypercholesterolemia, atherosclerosis, cardiac arrhythmias, depression, osteoporosis, hypothyroidism, goiter, thyroid cancer as well as glaucoma and congestive heart failure.

Detailed Description of the Invention

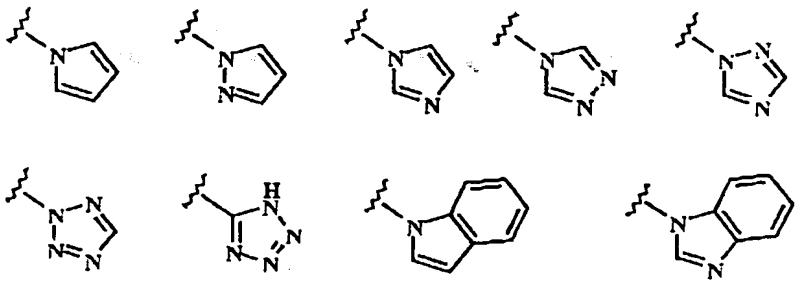
The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

The term "thyroid receptor ligand" as used herein is intended to cover any moiety which binds to a thyroid receptor. The ligand may act as an agonist, an antagonist, a partial agonist or a partial antagonist.

The term "aliphatic hydrocarbon(s) as used herein refers to acyclic straight or branched chain groups which include alkyl, alkenyl or alkynyl groups.

The term "aromatic hydrocarbon(s) as used herein refers to groups including aryl groups as defined herein.

The term "heteroaryl" or "heteroaromatic moiety" as used herein alone or as a part of another group refers to a 5- or 6-membered aromatic ring which includes 1, 2, 3, or 4 heteroatoms, one of which must be a nitrogen atom; the other atoms when present may be nitrogen, oxygen or sulfur, and such rings may be fused to another aryl or heteroaryl ring, and includes possible N-oxides. The heteroaryl group may optionally include 1 to 4 substituents such as aryl, alkyl, alkenyl, alkynyl, cycloalkyl, hydroxy, cyano, nitro, amino and/or carboxyl, and including the following



and the like.

Unless otherwise indicated, the term "lower alkyl", "alkyl" or "alk" as employed herein alone or as part of another group includes both straight and branched chain hydrocarbons, containing 1 to 12 carbons (in the case of alkyl or alk), in the normal chain, preferably 1 to 4 carbons, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, or isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, which may be optionally substituted with 1 to 4 substituents which may include alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, hydroxy, cyano, nitro, amino and/or carboxyl.

The term "aryl" as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl including 1-naphthyl and 2-naphthyl) and may be optionally substituted through available carbon atoms with 1, 2, or 3 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, hydroxy, amino, nitro, cyano and carboxylic acids.

Unless otherwise indicated, the term "lower alkenyl" or "alkenyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 12 carbons, preferably 2 to 5 carbons, in the normal chain, which include one to six double bonds in the normal chain, such as vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, and the like, which may be substituted as in the case of "alkyl".

Unless otherwise indicated, the term "lower alkynyl" or "alkynyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 12 carbons, preferably 2 to 8 carbons, in the normal chain, which include one triple bond in the normal chain, such as 2-propynyl, 3-butynyl, 2-butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonynyl, 4-decynyl,3-undecynyl, 4-dodecynyl and the like, which may be substituted as in the case of "alkyl".

Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated cyclic hydrocarbon groups or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups, containing one ring and a total of 3 to 7 carbons, preferably 3 to 5 carbons, forming the ring, which includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl and cyclohexenyl, , which may be substituted as in the case of "alkyl".

The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine as well as CF_3, with chlorine or bromine being preferred.

The compounds of formula I can be present as salts, in particular pharmaceutically acceptable salts. If the compounds of formula I have, for example, at least one basic center, they can form acid addition salts. These are formed, for example, with strong inorganic acids, such as mineral acids, for example sulfuric acid, phosphoric acid or a hydrohalic acid, with strong organic carboxylic acids, such as alkanecarboxylic acids of 1 to 4 carbon atoms which are unsubstituted or substituted, for example, by halogen, for example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, such as hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid, such as amino acids, (for example aspartic or glutamic acid or lysine or arginine), or benzoic acid, or with organic sulfonic acids, such as

(C_1-C_4) alkyl or arylsulfonic acids which are unsubstituted or substituted, for example by halogen, for example methyl- or ptoluene-sulfonic acid. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds of formula I having at least one acid group (for example COOH) can also form salts with bases. Suitable salts with bases are, for example, metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono, di or trilower alkylamine, for example ethyl, tertbutyl, diethyl, diisopropyl, triethyl, tributyl or dimethyl-propylamine, or a mono, di or trihydroxy lower alkylamine, for example mono, di or triethanolamine. Corresponding internal salts may furthermore be formed. Salts which are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or purification of free compounds I or their pharmaceutically acceptable salts, are also included.

Preferred salts of the compounds of formula I which include a basic groups include monohydrochloride, hydrogensulfate, methanesulfonate, phosphate or nitrate.

Preferred salts of the compounds of formula I which include an acid group include sodium, potassium and magnesium salts and pharmaceutically acceptable organic amines.

Preferred are compounds of the invention of formula I wherein R_1 is isopropyl;

R_2 and R_3 are independently halogen such as bromo or chloro; or

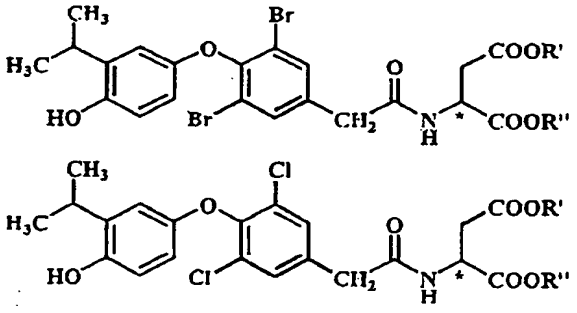
R_2 and R_3 are each methyl or one is methyl and the other is ethyl;

or one of R_2 and R_3 is halogen such as bromo or chloro, and the other is alkyl such as methyl, or hydrogen;

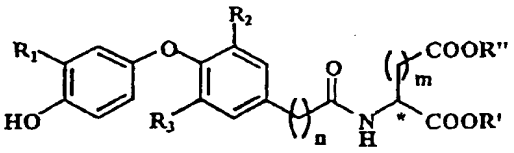
n is 0, 1 or 2; and

R_4 is carboxylic acid derivative of the type: amides, acylsulphonamides or an amino acid residue.

Preferred compounds of the invention have the structures:



and



wherein R_1=isopropyl, methyl, ethyl, cyclopentyl, cyclohexyl, and R_2 may be independently selected from Br, Cl and Me, n= 0, 1, 2 and 3, m= 0, 1, 2 and 3, * denotes either D or L stereochemistry and R' and R'' are independently selected from hydrogen, lower alkyl, especially ethyl and methyl, and where R' and R'' represent prodrug ester forms known in the art such as pivaloyloxymethyl or dioxolenylmethyl. Such prodrug esters are described in standard references such as Chapter 31, written by Camille G. Wermuth et al., in "The Practice of Medicinal Chemistry", ed. C. G. Wermuth, Academic Press. 1996 (and the references contained therein).

The compounds of formula I may be prepared by the exemplary processes described in the following reaction schemes. Exemplary reagents and procedures for these reactions appear hereinafter and in the working Examples.

Compounds of formula I of the invention can be prepared using the sequence of steps outlined in Schemes 1 to 5 set out below.

Scheme 1 depicts a synthesis of compounds of formula I in which R_4 = an amino acid, aniline derivative or aza containing heterocyclic ring, which through their nitrogen atom is connected to the aromatic ring by an intervening $(CH_2)_n$ group.

In Scheme 1, the amino acid, aniline derivative or aza containing heterocyclic ring, dissolved in a suitable solvent, is treated with 1-3 molar equivalents of an appropriate base, such as potassium carbonate, cesium carbonate, potassium hydroxide or sodium hydride. The resulting anion is then alkylated with the substituted iodide 5. Other combinations of alkylating agents or bases may be employed and are known to those skilled in the art. The reaction mixture is stirred at room temperature or heated until the starting materials are consumed. After standard work-up and purification, the methyl ether function is removed by treatment with 3-6 molar equivalents of a strong acid such as boron tribromide at 0°C to 25°C in an inert solvent such as dichloromethane. The reaction mixture gives after standard work-up and purification, the end products 6 (Examples 1-16).

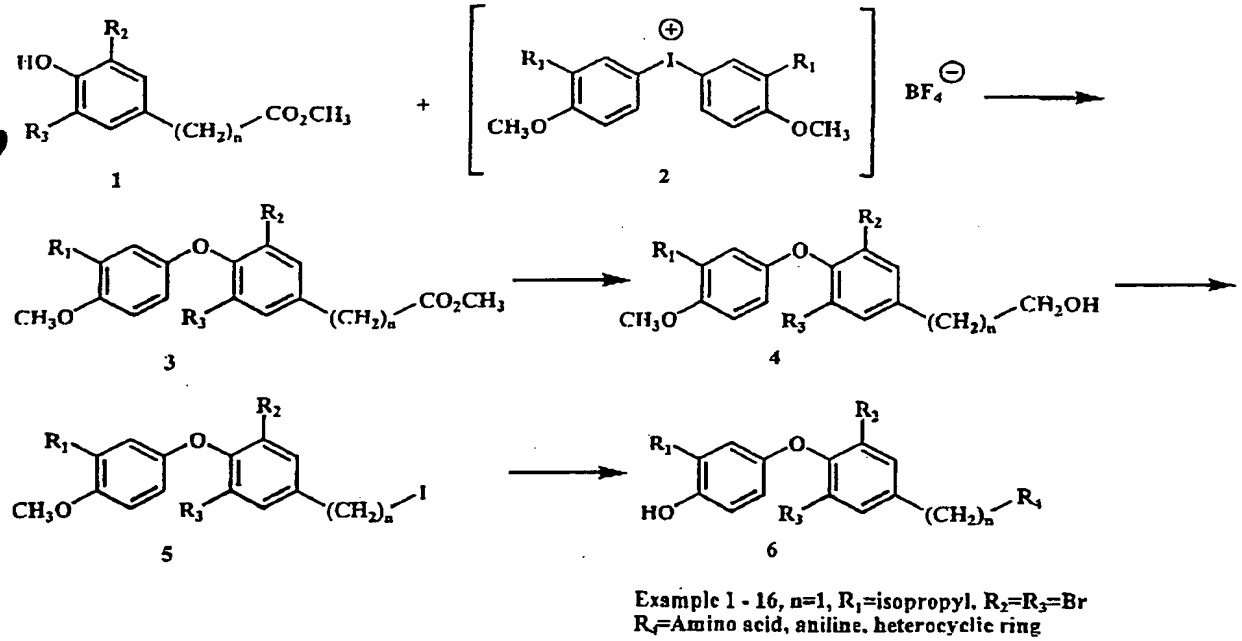
Scheme 1 also outlines the preparation of the intermediate iodide 5. An anisole-derived iodonium salt 2 and copper bronze in an inert solvent such as dichloromethane are mixed at room temperature. A mixture of the appropriate phenol ester 1 and a base such as triethylamine in an inert solvent such as dichloromethane was added to the mixture, generally using 2 molar equivalents each of the phenol and base, and 3 molar equivalents of iodonium salt 2. After stirring overnight at room temperature, the reaction mixture is purified via chromatography on silica gel, to give biaryl ether products 3. Other

methods exist in the literature for the synthesis of diaryl ethers, for example, two references directly apply to the synthesis of thyroid hormone analogs: D. A. Evans et al., Tet. Letters, volume 39, 2937-2940 (1998) and G. M. Salamonczyk et al., Tet. Letters, volume 38, 6965-6968 (1997). The carboxylic acid ester can be hydrolyzed with a mixture of aqueous sodium hydroxide and methanol. The methyl ether function can be removed by treatment of the free acid product of the previous procedure with 4-6 molar equivalents of a strong acid such as boron tribromide at 0°C in an inert solvent such as dichloromethane. Other combinations of protecting groups for the carboxylic acid present in 1 and phenolic hydroxyl in iodonium salt 2 can be employed, and their usage is known to those skilled in the art (references describing protecting group strategy include, for example, "Protecting Groups in Organic Chemistry", J. F. W. McOmie, Plenum Press, London, New York, 1973, and "Protective Groups in Organic Synthesis", T. W. Greene, Wiley, New York, 1984).

The intermediate ester product 3 is reduced by treatment with an appropriate reducing agent such as diisobutyl aluminium hydride in an inert solvent such as tetrahydrofuran at 0°C. If R_2 and R_3 are alkyl, then lithium aluminum hydride may be employed without the risk of reducing away halogen substituents at those positions. Standard work-up and purification yields the desired alcohol product 4. Other reducing agents may be employed and are known to those skilled in the art.

Intermediate 4 in Scheme 1 is finally converted to the intermediate iodide 5 by treatment of alcohol 4 with 2 molar quivalents of sodium iodide, phosphorous pentaoxide and phosphorous acid, and heated at 120°C for 15 minutes. Numerous other methodologies for conversion of simple hydroxyl groups to the corresponding alkyl iodides are well known to those skilled in the art.

Scheme 1

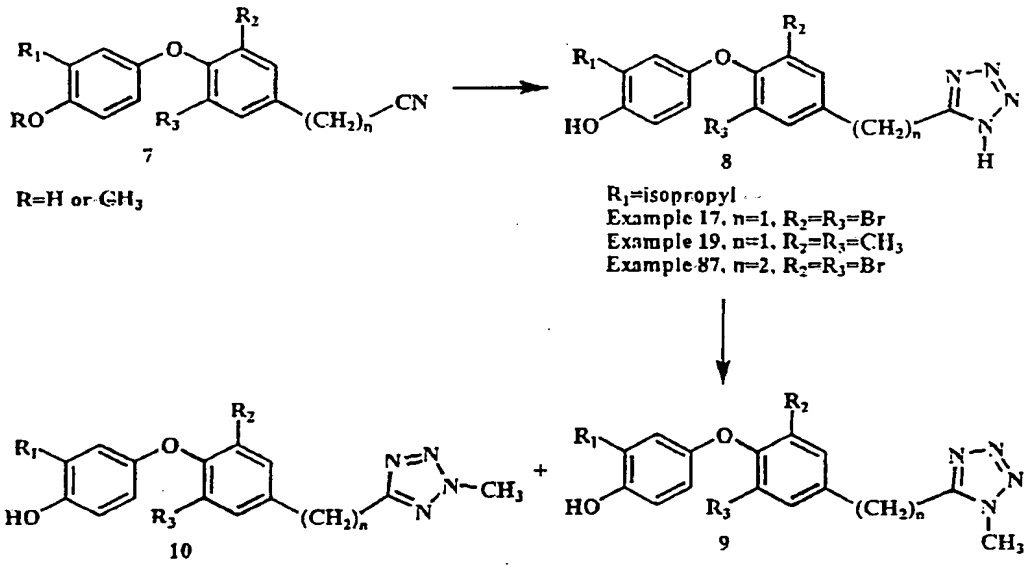


Example 1 - 16, n=1, R_1=isopropyl, R_2=R_3=Br
R_4=Amino acid, aniline, heterocyclic ring

Scheme 2 depicts a synthesis of compounds of formula I in which R_4 is a tetrazole ring. Phenylacetonitrile 7 is readily prepared from benzylic iodide 5 by standard means such as reaction with sodium cyanide in a solvent mixture such as water/ethanol. Reaction of phenylacetonitrile 7, with sodium azide and ammonium chloride in dimethylformamide at elevated temperatures gives tetrazole derivatives 8 (Example 17, 19 and 87), after standard work-up and purification procedures. In Example 87 this step was followed by a standard demethylation procedure, as above, in order to remove the protecting group.

Examples of substituted tetrazoles that can be prepared by further chemistry are also depicted in Scheme 2. Tetrazole derivative 8 (Example 17) can for instance be treated with an appropriate base such as sodium hydrogen carbonate in acetone, followed by N-alkylation with methyl iodide to afford derivatives 9 and 10 (Example 18), after standard work-up and purification procedures. Other alkylating agents and bases may be employed and are known to those skilled in the art.

Scheme 2



7 8

10 9

Example 18, R_1=isopropyl, n=1, R_2=R_3=Br

Examples of compounds of formula I in which R_4 is an amide produced by coupling to an amino acid are shown in Scheme 3. The following procedures all involve the coupling of benzoic acid derivative 11 (n=0), with its phenolic hydroxyl group either protected by a methyl, left unprotected or bound to a resin, with various protected amino acids, to afford the corresponding amides 12 of 3,5-dihalo-4-(4-hydroxy-3-isopropylphenoxy)carboxylic acids. The carboxylic acids 11 are readily obtained, for example, by hydrolysis of the corresponding esters 3.

In one procedure, a mixture of 11 with R=Me, a coupling reagent such as 3-ethyl-1-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI), and a base such as 1-hydroxybenzotriazole hydrate (HBT) in dimethylformamide is stirred at room temperature. The appropriate protected amino acid and triethylamine is added. The reaction mixture yields after work-up and purification by either chromatography or recrystallization the corresponding coupled material, which after standard demethylation and hydrolysis procedures, gives the desired final amide products (Examples 20 and 24).

In another more fruitful modification of the same procedure as above, 11 is kept unprotected (R=H) from the beginning of the sequence to give, after basic hydrolysis and standard work-up and purification procedures, other examples of carboxylic acid amides (Example 22-23, 28, 71-72, 74, 80-81, 83-84).

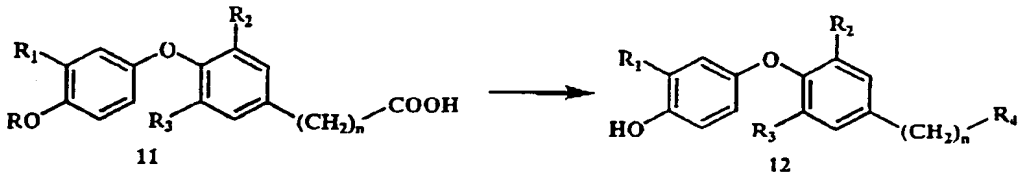
Amide end-products which contain free carboxylic acid groups can be re-esterified by standard procedures by, for instance, heating them in a mixture of refluxing methanol and thionyl chloride, to give the corresponding methyl acid ester derivatives (Examples 21 and 82).

An amide library can also be prepared by solid phase synthesis (Examples 30-55). In this procedure a methyl ester of intermediate 11 is loaded on a resin such as a Merrifield resin by standard procedures, well known to those skilled in the art. The resulting resin is then treated with sodium hydroxide in methanol to provide the resin-bond free carboxylic acid form of 11. Each resin pin is then filled with a solution of the corresponding aminoacid ester, PyBOP (benzotriazole-1-yl-oxy-tris-pyrrolidino phosphonium hexafluorophosphate), HBT, and N,N-diisopropylethylamine (Hunig's base, DIEA) and an inert solvent such as dichloromethane and is stirred at room temperature for days. Other combinations of base and coupling reagents can be employed here with successful results. After treatment of each of the individual pins with an appropriate base such as aqueous potassium hydroxide and washing of the resin, the amides are disassembled from the resin by treatment of a mixture of trifluoroacetic acid, dimethylsulfite and water.

Several other related methodologies exist for the coupling of amino acids with aromatic, as well as non-aromatic, carboxylic acids in solution or solid phase and are known to those skilled in the art.

The amino acid product 12 can reduced by treatment with an appropriate reagent such as sodium borohydride in an polar solvent such as ethanol at room temperature. If R_2 and R_3 are alkyl, then lithium aluminum hydride may be employed without the risk of reducing the halogen substituents at those positions. Standard work-up and purification yields the desired alcohol product (Example 29). Other reducing agents may be employed and are known to those skilled in the art.

Scheme 3



R= Me, H or resin

R_1=isopropyl, R_4=C(=O)—Amino acid

Example 20-25, 28, 30-55, n=0, R_2=R_3=Br
Example 71-72, n=1, R_2=R_3=Br
Example 74, n=1, R_2=R_3=Cl
Example 80-84, n=2, R_2=R_3=Br

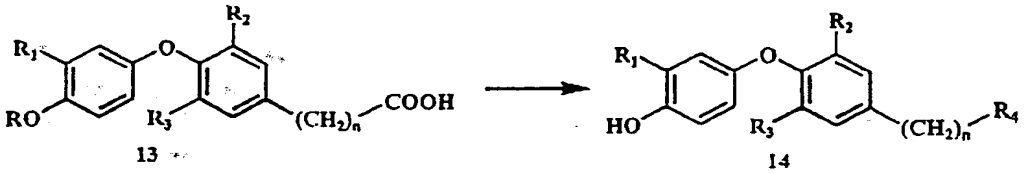
Scheme 4 depicts a synthesis of compounds of formula I in which R_4 is an acylsulphonamide. Similar procedures as for the coupling of amino acids above are employed.

In one procedure, a mixture of 13 with R=Me, a coupling reagent such as 3-ethyl-1-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI), and a base such as dimethylaminopyridine (DMAP) and the appropriate sulphonamide in dichloromethane is stirred at room temperature. The reaction mixture yields after work-up and purification by either chromatography or recrystallization the corresponding coupled material, which after standard demethylation procedures, affords the desired acylsulphonamide (Examples 56-57, 85-86).

In another procedure, 13 is kept unprotected (R=H), mixed with a base such as DIEA and the appropriate sulphonamide in dichloromethane. Dimethylformamide is added to the mixture if the sulphonamide does not solve completely. Treatment of the mixture with a base and coupling reagent combinations such as HOBt and PyBOP, gives after heating and subsequent mild acid treatment during work-up and purification by HPLC, yet other examples acylsulphonamides (Example 58-70).

Other combinations of protecting groups and procedures can be employed. For example, applying similar chemistry as in Examples 56-57 and 85-86 above , but with R= $Si(CH_3)_2t$-Bu, gives further examples of acylsulphonamides after removal of the protecting silyl group with ammonium flouride (Examples 88-91).

Scheme 4



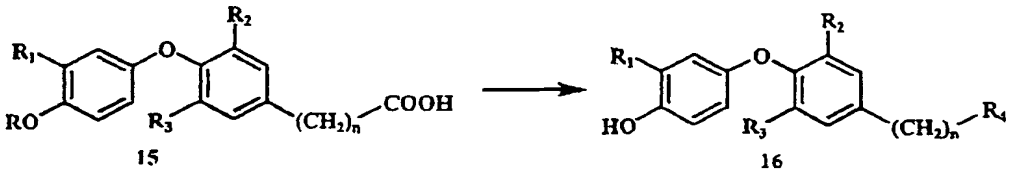
The procedures described in Scheme 5 further exemplify methods for the synthesis of compounds of formula I. Several structurally diverse amides, primary as well as secondary, were prepared as outlined in Scheme 5. Many alternative procedures for the coupling of amino acids above can be employed and are well known to those skilled in the art.

For example, in one procedure secondary diacetic acids amides are obtained through the treatment of 15 by dimethyliminodiacetate and EDCI in dimethylformamide or dichloromethane, followed by standard work-up procedures and final basic hydrolysis of the ester function (Example 73, 76-79).

In another procedure, primary aromatic amines were obtained by an similar procedure as in Example 20 above (Example 26-27).

A library comprising 100 diverse primary and secondary amides was also prepared in an automated fashion, using standard literature methods (Example 92-191).

Scheme 5



With respect to the above reaction schemes, although the various R_1, R_2, R_3, R_4 and n moieties are specifically defined, unless otherwise indicated, it is to be understood that R_1, R_2, R_3, and R_4 may be any of the groups encompassed thereby and n may be 0, 1, 2, 3 or 4.

The compounds of the invention are agonists, that are preferably selective for the thyroid hormone receptor-beta, and as such are useful in the treatment of obesity, hypercholesterolemia and atherosclerosis by lowering of serum LDL levels, alone or in combination with a lipid modulating drug such as an HMG-CoA reductase inhibitor, fibrate, thiazolidinedione, or MTP inhibitor, amelioration of depression alone or in combination with an antidepressant, and stimulation of bone formation to treat osteoporosis in combination with any known bone resorption inhibitor such as alendronate sodium. In addition, the compounds of the invention may be useful as replacement therapy in elderly patients with hypothyroidism or subclinical hypothyroidism who are at risk for cardiovascular complications, in the treatment of the elderly to provide a sense of well-being, and in the treatment of non-toxic goiter; in the management of papillary or follicular thyroid cancer (alone or with T_4); in the treatment of skin disorders such as psoriasis, glaucoma, cardiovascular disease such as in the prevention or treatment of atherosclerosis, and congestive heart failure.

The compounds of the invention may also be used to treat skin disorders or diseases involving dermal atrophy such as glucocorticoid induced dermal atrophy, including restoration of dermal atrophy induced by topical glucocorticoids, the prevention of dermal atrophy induced by topical glucocorticoids (such as the simultaneous treatment with topical

glucocorticoid or a pharmacological product including both glucocorticoid and a compound of the invention), the restoration/prevention of dermal atrophy induced by systemic treatment with glucocorticoids, restoration/prevention of atrophy in the respiratory system induced by local treatment with glucocorticoids, UV-induced dermal atrophy, or dermal atrophy induced by aging (wrinkles, etc.), wound healing, keloids, stria, cellulite, roughened skin, actinic skin damage, lichen planus, ichtyosis, acne, psoriasis, Dernier's disease, eczema, atopic dermatitis, chloracne, pityriasis and skin scarring.

In treating skin disorders or diseases as described above, the compounds of the invention may be used in combination with a retinoid or a vitamin D analog.

The compounds of the invention can be administered orally or parenterally such as subcutaneously or intravenously, as well as by nasal application, rectally or sublingually to various mammalian species known to be subject to such maladies, e.g., humans, cats, dogs and the like in an effective amount within the dosage range of about 0.1 to about 100 mg/kg, preferably about 0.2 to about 50 mg/kg and more preferably about 0.5 to about 25 mg/kg (or from about 1 to about 2500 mg, preferably from about 5 to about 2000 mg) on a regimen in single or 2 to 4 divided daily doses.

The active substance can be utilized in a composition such as tablet, capsule, ointment, hydrophilic ointment, cream, lotion, solution or suspension or in other type carrier materials such as transdermal devices, iontophoretic devices, rectal suppositories, inhalant devices and the like. The composition or carrier will contain about 5 to about 500 mg per unit of dosage of a compound of formula I. They may be compounded in conventional matter with a physiologically acceptable vehicle or carrier, excipient, binder, preservative, stabilizer, flavor, etc., as called for by accepted pharmaceutical practice.

The following working Examples represent preferred embodiments of the present invention. The ^{1}H NMR spectra was all consistent with the assigned structures in Example 1-87.

Example 1

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]aspartic acid.

(a) To a suspension of bis(3-isopropyl-4-methoxyphenyl)iodonium tetrafluoroborate (prepared by the method of Yokayama et al, Journal of Medicinal Chemistry 1995, 38, 695-707) (37 g) and copper bronze (6.1 g) in dichloromethane (150 ml), was added a solution of methyl 3,5-dibromo-4-hydroxybenzoate (15 g) and triethylamine (5.4 g) in dichloromethane (100 ml) dropwise at room temperature. The mixture was stirred overnight and then filtrated through Celite. After concentration, the resulting residue was passed through a short silica gel column eluted with ethyl acetate/light petroleum ether (5/95). The pure fractions were pooled and concentrated to dryness. The residue was recrystallized from

methanol affording 19.5 g (89%) of methyl 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)-benzoate.

b) The above methyl ester (4.6 g) was treated with a 1 M solution of diisobutyl aluminium hydride in tetrahydrofuran (40 ml) at 0°C and then warmed to room temperature and stirred for 1 hour. The reaction mixture was poured into an ice-cold 1 M hydrochloric acid solution and extracted with ethyl acetate 3 times. The organic layer was washed (brine), dried, filtered and concentrated to dryness affording 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzylalcohol (4.15 g, 96%) as oil which became a white solid after standing.

c) The above alcohol (215 mg) was added into a mixture of phosphorus pentoxide (36 mg) and phosphorous acid (490 mg) followed by addition of sodium iodide (150 mg). The mixture was stirred at 120°C for 15 min and then partitioned between water and ethyl acetate. The organic layer was washed with an aqueous solution of sodium thiosulphate and brine, dried, filtered and concentrated. The residue was crystallized from petroleum ether to give 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzyliodide (170 mg, 63%).

d) 3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzyl iodide (400 mg) was stirred under reflux with *L*-*t*-butyl aspartate (218 mg) and potassium carbonate (410 mg) in acetonitrile for 4 hours. The solids was removed by filtration and the organic phase was washed with water, dried, filtered and concentrated. The residue was chromatographed on silica gel eluted with ethyl acetate/ petroleum ether (1:8). Pure fractions were concentrated to give L-*t*-butyl N-[3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzyl]aspartate (430 mg, 94%).

e) The above ester (297 mg) was treated with boron tribromide (1 M in dichloromethane, 4.8 ml) at 0°C and the mixture was stirred overnight at room temperature before ice/water was added. The water layer was acidified (pH = 5-6) and extracted with ethyl acetate 3 times. The organic layer was dried, filtered and concentrated and the residue was crystallized from light petroleum ether to give *L*-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]aspartic acid (92 mg, 37%).

Example 2

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-4-hydroxyaniline.

a) A mixture of 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzyl iodide (400 mg), 4-methoxyaniline (110 mg) and potassium carbonate (410 mg) in acetonitrile (20 ml) was stirred under reflux for 4 hours. The reaction mixture was partitioned between water and acetonitrile. The organic layer was dried, filtered and concentrated. The residue was chromatographed on silica gel eluted with ethyl acetate/petroleum ether (1:10) to give

N-[3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzyl]-4-methoxyaniline (350 mg. 88%).

b) The above methoxy compound (200 mg), in dichloromethane, was treated with boron tribromide (1 M in dichloromethane, 2.3 ml) at 0°C. The mixture was stirred overnight at room temperature before ice/water was added. The layers were separated and the water layer was extracted with dichloromethane. The combined organic layer was dried, filtered and concentrated. The crude product was chromatographed on silica gel eluted with ethyl acetate/petroleum ether (1:4) to give N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)-benzyl]-4-hydroxyaniline as yellow solid which was recrystallized from dichloromethane and petroleum ether affording 95 mg of crystalline solid (51%).

Example 3

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]phthalimid.

To a solution of potassium hydroxide (34 mg, 0.6 mmol) in 5 ml of 75% ethanolic benzenephtalimide (89 mg, 0.6 mmol) and 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)-benzyl iodide (270 mg, 0.5 mmol) was added. The reaction mixture was refluxed until the starting materials were consumed, concentrated and poured into a saturated solution of sodium chloride. Ethyl acetate was added and the phases were partitioned. The aqueous phase was extracted twice with ethyl acetate, toluene was added and the combined phases were concentrated. The residue was dissolved in 10 ml of dichloromethane, kept under nitrogen and cooled to -40°C. To the solution was added 1.0 ml of 1 M boron tribromide (1.0 mmol, solution in dichloromethane). After 16 hours at room temperature the reaction mixture was treated with a saturated sodium chloride solution of 1 M hydrochloric acid, the phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic phase was dried over magnesium sulphate, filtered and concentrated. The crude product was purified on a chromatotron (silica gel, 8:2 petroleum-ether/ethyl acetate) to give 62 mg (23%) of N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]phthalimid.

Example 4

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]hydantoin.

Hydantoin (60 mg, 0.6 mmol) was alkylated with 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzyl iodide and demethylated using the method described in Example 3. The crude product was purified on a chromatotron (silica gel, 99.5:0.5:0.1 chloroform/ethanol/acetic acid) to give 207 mg (69%) of N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]hydantoin.

Example 5

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]pyrrazole.

Pyrazole (34 mg, 0.5 mmol) dissolved in 0.5 ml of dry tetrahydrofuran was added to a stirred solution of sodium hydride (20 mg, 0.52 mmol) in 0.5 ml dry tetrahydrofuran under nitrogen. After one hour, the reaction mixture was cooled down to 0°C and 3,5-dibrom-4-(4-methoxy-3-isopropylphenoxy)benzyl iodide (270 mg, 0.5 mmol) in 0.5 ml tetrahydrofuran was added dropwise. The reaction mixture was stirred overnight, quenched with a saturated solution of sodium chloride and diluted with ethyl acetate. The phases were partionated and the aqueous phase was extracted twice with ethyl acetate, toluene was added and the combined phases were concentrated. The residue was dissolved in 10 ml of dichloromethane, kept under nitrogen and cooled to -40°C. To the solution was added 1.0 ml of 1M boron tribromide (1.0 mmol, solution in dichloromethane). After 16 hours at room temperature the reaction mixture was treated with a saturated sodium chloride solution of 1 M hydrochloric acid, the phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic phase was dried over magnesium sulphate, filtered and concentrated. The residue was purified on a chromatotron (silica gel, 9:1:0.1 chloroform /metanol/acetic acid) to give 86 mg (37%) of N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]pyrrazole.

Example 6

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]imidazole

Imidazole (34 mg, 0.5 mmol) was alkylated with 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzyl iodide and demethylated using the method described in Example 5. The residue was purified on a chromatotron (silica gel,7:3 petroleum ether/ethyl acetate) to give 99 mg (43%) of N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]imidazole.

Example 7

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]4-azabenzimidazole

4-Azabenzimidazole (60 mg, 0.5 mmol) was alkylated with 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzyl iodide and demethylated using the method described in Example 5. The residue was purified on a chromatotron (silica gel, 96:4:0.5 chloroform/methanol/acetic acid) to give 79 mg (31%) of N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-4-azabenzimidazole as a yellow foam.

Example 8

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-4-imidazole carboxylic acid

Methyl 4-imidazole carboxylate (70 mg, 0.5 mmol) was alkylated with 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzyl iodide and demethylated using the method described in Example 5. The ester was hydrolyzed simultaneously in the demethylation step. The acid was purified on the chromatotron (silica gel, 9:1:0.1 chloroform/ methanol/acetic acid) to give 10 mg (4%) of N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-4-imidazole carboxylic acid.

Example 9

1-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-4-methyl-5-imidazole carboxylic acid

Ethyl 4-methyl-5-imidazole carboxylate (77 mg, 0.5 mmol) was alkylated with 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzyl iodide and demethylated using the method described in Example 5. The ester was hydrolyzed simultaneously in the demethylation step. The acid was purified on the chromatotron (silica gel, 98:2:0.03 chloroform/methanol/acetic acid) and subsequently washed with ethyl acetate to give 226 mg (86%) of 1-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-4-methyl-5-imidazole carboxylic acid.

Example 10

Ethyl 1-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-4-pyrazole carboxylate

Ethyl 4-pyrazole carboxylate (70 mg, 0.5 mmol) was alkylated with 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzyl iodide and demethylated using the method described in Example 5. The ester was purified on a chromatotron (silica gel, 99:1:0.1 chloroform/methanol/acetic acid) to give 139 mg (52%) of ethyl 1-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-4-pyrazole carboxylic acid.

Example 11

1-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-4-pyrazole carboxylic acid

A mixture of ethyl 1-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-4-pyrazole carboxylate (Example 10) (54 mg, 0.1 mmol), 1ml of 1M sodium hydroxide and 1.5 ml of methanol was stirred at room temperature for 24 hours. The reaction mixture was then acidified with 1M hydrochloric acid and a precipitate was aggregated. The precipitate was triturated with petroleum ether, filtered, triturated with petroleum ether and diethyl ether and

dried at room temperature *in vacuo* to give 43 mg (80 %) of 1-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-4-pyrazole carboxylic acid.

Example 12

Ethyl 1-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-3-trifluoromethyl)pyrazole-4 carboxylate

Ethyl-(3-trifluoromethyl)pyrazole-4-carboxylate (104 mg, 0.5 mmol) was alkylated with 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzyl iodide and demethylated using the method described in Example 5. The ester was purified on a chromatotron (silica gel, 96:4:0.3 chloroform/methanol/acetic acid) to give 111 mg (37%) of ethyl 1-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-3-trifluoromethyl)pyrazole-4 carboxylate as a dark yellow solid.

Example 13

1-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-3-trifluoromethyl)pyrazole-4 carboxylic acid

Ethyl 1-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-3-trifluoromethyl)pyrazole-4 carboxylate (Example 12) (61 mg, 0.1 mmol) was hydrolyzed using the method described in Example 12. The residue was purified on a chromatotron (silica gel, 98:2:0.3 chloroform/ methanol/acetic acid) to give 56 mg (97%) of 1-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-3-trifluoromethyl)pyrazole-4 carboxylic acid as an yellow oil.

Example 14

1-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-(3-methyl)pyrazole-5-carboxylic acid.

Ethyl 3-methylpyrazole-5-carboxylate (77 mg, 0.5 mmol) was alkylated with 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzyl iodide and demethylated using the method described in Example 5. The ester was hydrolyzed simultaneously in the demethylation step. The acid was purified on a chromatotron (silica gel, 9:1:0.1 chloroform/ methanol/acetic acid) to give 140 mg (53%) of 1-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-(3-methyl)pyrazole-5-carboxylic acid as pale yellow solid. Mp: >270°C (dec.).

Example 15

1-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-5-azabenzimidazole

A mixture of 5-azabenzimidazole (60 mg, 0.5 mmol), cesium carbonate (489 mg, 1.5 mmol), and 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzyl iodide (405 mg, 0.75 mmol) in 5 ml of dimethyl formamide was stirred at room temperature for 40 minutes. The reaction mixture was poured into diethyl ether and washed once with water. The organic phase was dried over magnesium sulphate, filtered and concentrated. The residue was dissolved in 10 ml of dichloromethane, kept under nitrogen and cooled to -40°C. To the solution was added 1.0 ml of 1M boron tribromide (1.0 mmol, solution in dichloromethane). After 16 hours at room temperature the reaction mixture was treated with a aqueous solution of saturated sodium chloride and 1 M hydrochloric acid, the phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic phase was dried over magnesium sulphate, filtered and concentrated. The residue was purified on the chromatotron (silica gel, 98:2:1 chloroform/methanol/acetic acid) to give 51 mg (20%) of 1-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-5-azabenzimidazole.

Example 16

1-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-6-azabenzimidazole

5-Azabenzimidazole (60 mg, 0.5 mmol), was alkylated with 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzyl iodide (405 mg, 0.75 mmol) using the method described in Example 15 to give 81 mg (31%) of 1-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-6-azabenzimidazole.

Example 17

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyltetrazole.

Ammonium chloride (42 mg, 0.776 mmol) and sodium azide (50 mg, 0.776 mmol) was added to a stirred and refluxing solution of 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzylcyanide (33mg, 0.0776 mmol) in 1.0 ml of dimethyl formamide. After 2.5 hours the reaction mixture was concentrated, treated with 6 M hydrochloric acid and extracted several times with ethyl acetate. The combined organic phases were dried over magnesium sulphate, filtered and concentrated. The residue was purified by column chromatography (silica gel, 96:4:1 chloroform/methanol/acetic acid) to give 23mg (63%) of 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyltetrazole.

Example 18

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl(1-methyl)tetrazole and 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl(2-methyl)tetrazole.

A mixture of 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyltetrazole (Example 17) (15 mg, 0.032 mmol), sodium bicarbonate (18 mg , 0.128 mmol) and methyl iodide (18 mg, 0.128 mmol) in acetone (1 ml) was refluxed for 6 hours. The reaction mixture was concentrated, diluted with ethyl acetate and washed twice with 1M sodium hydroxide. The organic phase was dried over magnesium sulphate, filtered and concentrated. The residue was purified on a chromatotron (silica gel, 98:2:0.3 chloroform/methanol/ acetic acid) to give 12 mg (78%) of 3 ,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl(2-methyl)tetrazole and 6 mg (39%) of 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl(1-methyl)tetrazole.

Example 19

3,5-Dimethyl-4-(4-hydroxy-3-isopropylphenoxy)benzyltetrazole.

To a stirred solution of 3,5-dimethyl-4-(4-hydroxy-3-isopropylphenoxy)phenylacetonitrile (154 mg) in 6.3 ml of dimethyl formamide, ammonium chloride (297 mg, 5.21 mmol) and sodium azide (339 mg, 5.21 mmol) was added at reflux. After 4.5 hours the reaction mixture was concentrated, treated with 6 M hydrochloric acid and extracted several times with ethyl acetate. The combined organic phases were dried over magnesium sulphate, filtered and concentrated. The residue was purified by column chromatography (silica gel, 96:4:1 chloroform/methanol/acetic acid) to give 68 mg (37%) of the title compound.

Example 20

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]aspartic acid.

(a) A solution of 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (200 mg), 3-ethyl-1-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI), (95 mg), 1-hydroxybenzotriazole hydrate (HBT), (91 mg) in dimethyl formamide (5 ml) was stirred at room temperature for 0.5 h followed by addition of a solution of *L*-di-*t*-butyl aspartate hydrochloride (166 mg) and triethylamine (100 mg) in dimethyl formamide (2 ml). After stirring for one hour, the mixture was partitioned between water and chloroform. The organic phase was dried, filtered and concentrated. The residue was chromatographed on silica gel eluted with ethyl acetate/light petroleum ether (1:4). Pure fractions were pooled and concentrated to give *L*-di-*t*-butyl N-[3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoyl]aspartate (260 mg, 86%).

(b) The above methoxy compound (502 mg) was demethylated and hydrolyzed using the method described in Example 2(b) to give *L*-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl] aspartic acid (239 mg, 59%) which could be crystallized from ethyl acetate and petroleum ether.

Example 21

L-Dimethyl N-[3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoyl] aspartate

L-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl] aspartic acid (Example 20b) (330 mg) was refluxed in methanol with a few drops of thionyl chloride for three days. Concentration and column chromatography on silica gel (ethyl acetate/petroleum ether = 1:4) gives *L*-Dimethyl N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]aspartate (190 mg, 53%).

Example 22

D-Dimethyl N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]aspartate

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoic acid (300 mg) was coupled with *D*-dimethyl aspartate hydrochloride (169 mg) using the method described in Example 20(a) to give *D*-dimethyl N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]aspartate (275 mg, 73%).

Example 23

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]aspartic acid

D-Dimethyl N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]aspartate (Example 22, 200 mg) was hydrolyzed by treatment with 1 M aqueous sodium hydroxide (2 ml) in methanol (4.5 ml). The crude product was crystallized from ethyl acetate and petroleum ether to give 185 mg (97%) of *D*-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]aspartic acid.

Example 24

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]glutamic acid

a) 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid was coupled with *L*-di-*t*-butyl glutamate hydrochloride (887 mg) using the method and purification described in Example 20(a) to give *L*-di-*t*-butyl N-[3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoyl]glutamate (1.24 g, 91%).

b) The above methoxy compound (500 mg) was demethylated and hydrolyzed using the method described in Example 2(b) to give *L*-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]glutamic acid (248 mg, 58%).

Example 25

L-Dimethyl N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]glutamate

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]glutamic acid (Example 24) (248 mg) was esterified using the method described in Example 21 to give *L*-dimethyl N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]glutamate (230 mg, 88%).

Example 26

3-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]aminobenzoic acid

a) 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoate (444 mg) was coupled with methyl 3-aminobenzoate (227 mg) using the method and purification described in Example 20(a) to give 460 mg (86%) of methyl 3-[3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoyl]aminobenzoate.

b) The above methoxy compound (340 mg) was demetylated and hydrolysed using the method described in Example 2(b) to give 41 mg (13%) of 3-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]aminobenzoic acid and 230 mg (70%) of 3-[3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy) benzoyl]aminobenzoic acid

Example 27

4-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]aminobenzoic acid

a) 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (444 mg) was coupled with methyl 4-aminobenzoate (227 mg) using the method and purification described in Example 20(a) to give 249 mg (46%) of methyl 4-[3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoyl]aminobenzoate.

b) The above methoxy compound (50 mg) was demethylated and hydrolyzed using the method described in Example 2(b) to give 32 mg (68%) of 4-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]aminobenzoic acid.

Example 28

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]alanine.

a) 3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoic acid (215 mg) was coupled with L-alanine methyl ester hydrochloride (84mg) using the method described in Example 20(a) to give 110 mg (43%) of *L*-methyl N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]alaninc.

b) The above ester was hydrolyzed using the method described in Example 23 to give 73 mg (68%) of *L*-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]alanine.

Example 29

L-2-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]amino-1,4-butadiol

A suspension of *L*-Dimethyl N-[3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)-benzoyl]aspartate (Example 21, 50 mg) and sodium borohydride (40 mg) in 99.5% ethanol was stirred at room temperature overnight. The mixture was acidified with 10% Hydrochloric acid and partitioned between water and ethyl acetate. The resulting residue was purified by column chromatography on silica gel eluted with ethyl acetate. Pure fractions were pooled and concentrated. The residue was recrystallized from ethyl acetate and petroleum ether to give 35 mg (78%) of *L*-2-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]amino-1,4-butadiol.

General procedure for the preparation of the amino acid library by solid phase synthesis (Examples 30-55)

Loading of the resin with 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy benzoic acid:

A mixture of methyl 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoate (7.6g, 17.1mmol), Merrifield resin (5g, 1.2mmol/g) and sodium hydride (432 mg, 18 mmol) in 100 ml of dimethyl formamide was stirred in a 250 ml round flask at 50 °C for 40 hours. After cooling, the mixture was filtered and the resin was washed with water (3x 10 ml), dimethyl formamide (3x10 ml), ethyl acetate(3x10 ml) and dichloromethane(3x10 ml). The resulting resin was dried in vacuum overnight to give 8.54g of resin, loaded with the methyl ester.

To the resin was added methanol (100 ml) and an aqueous solution of sodium hydroxide (100 ml, 1M). The suspension was stirred under at 80°C for one day, cooled to room temperature and filtered. The resin was washed with water (3x10 ml), TETRAHYDROFURAN (3x10 ml), ethyl acetate (3x10 ml) and dichloromethane(3x10 ml). After drying under vacuum, 5.94 g of resin loaded with the title compound was obtained.

Determination of the loading capacity of the resin:

The resin (100 mg) was treated with a mixture of trifluoroacetic acid, dimethyl sulphite and water (85:15:5). The mixture was stirred at room temperature for two days. The resin was removed by filtration and the organic phase was collected and concentrated under vacuum. The resulting residue was chromatographed on silica gel (methanol/chloroform/ acetic acid 10:90:1). The pure fractions were pooled and concentrated affording 17.5 mg (51%) of 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoic acid as white solid. The loading rate was estimated as 0.04 mmol (17,5 mg) per 100 mg of loaded resin.

Coupling of 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy) benzoic acid to different amino acids

DIVERSOMER® 8-100 synthesizer was used for syntheses and Savant SpeedVac® system for concentration.

To each of eight PINs was added 100 (±5) mg of the loaded resin (17.5 mg /100 mg; 0.04 mmol/100 mg). The resin-filled PINs were placed in the holder block. Eight vials (12 ml) were placed into the reservoir rack, equipped with a magnetic stir bar and filled with a mixture consisting of the corresponding aminoacid ester (0.4 mmol). PyBOP (104 mg, 0.2 mmol), HBT (27 mg, 0.2 mmol), DIEA (52 mg, 0.4 mmol) and dichloromethane (5 ml). The holder block was assembled with the reservoir rack. The reaction was carried out at room temperature with stirring for two days. The reservoir rack was disassembled from the holder block. Each resin in the PINs was dispended with 2 ml each of dimethyl formamide, water, ethyl acetate and dichloromethane. The washing procedure was repeated twice. The resin in PINs was finally dried by pressed air-flow.

Eight new vials (12 ml) were placed into the reservoir rack and each vial was equipped with a magnetic stir bar. The holder block was assembled with the reservoir rack. A methanolic solution of KOH (5 ml, 2 M) was in 1 ml increments down through the inside of each PIN. The apparatus was allowed to stand in a fume hood with stirring for two days. The synthesizer was disassembled and the resins were washed with water (4x2 ml), methanol (4x2 ml) and dichloromethane (4x2 ml). The resin in PINs was dried by pressed air-flow.

The holder block was reassembled from the reservoir rack. A 50 ml stock solution of trifluoroacetic acid/dimethyl sulphite/water(85:15:5; v/v) was prepared. The solution (5 ml) was added to each of the eight PINs in 1 ml increments. The apparatus was allowed to stand in a fume hood with stirring for 2 days. The resercoir rack and the holder block was disassembled. Each PIN was washed with 1 ml of the above solution. The contents of the 8 reservoir vials were concentrated to dryness. Each vial was partitioned between aqueous

Hydrochloric acid (1 ml, 1 M) and ethyl acetate (2 ml). The content of the eight reservoir vials were carefully transferred into the eight drying cartridges (Chem elute CE1003, VARIAN), equipped with test tubes underneath. The cartridges were allowed to drain by gravity, rinsed with ethyl acetate (3x1.5 ml) after 5 min and finally forced to drain under reduced pressure. The organic layer was collected and concentrated to give the following products in the yields mentioned below.

Example 30

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]valine

12.2mg (57.7%)

Example 31

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]leucine

20.1mg (92.5%)

Example 32

L-S-Benzyl, N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]cysteine

14.9mg(60%)

Example 33

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]tyrosine

5.9mg(24.8%)

Example 34

L-N-δ-(2,2,5,7,8-Pentamethylchroman-6-sulfonyl),
N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]arginine

10.7mg(31%)

Example 35

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]aminobutyric acid (Example 88).

15.6mg(75,5%)

Example 36

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]valine (Example 89).

19.7mg(93%)

Example 37

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]leucine (Example 90).

14.8mg(68%)

Example 38

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]proline (Example 91).

8.6mg(41%)

Example 39

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]cysteine (Example 92).

2.88mg(13.5%)

Example 40

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]glycine

15.8mg(81%)

Example 41

L-N-α-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]lysine

23.5mg(105%)

Example 42

D-N-α-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]lysine (Example 95).

24.9mg(112%)

Example 43

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]aminoisobutyric acid

6.72mg(32.6%)

Example 44

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]phenylglycine (Example 97).

7.1mg(31%)

Example 45

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]phenylglycine (Example 98).

15.1mg(67%)

Example 46

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]sarcosine (Example 99).

6.7mg(33.4%)

Example 47

DL-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]-α-methylphenylalanine (Example 100).

7.4mg(31.4%)

Example 48

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]isoleucine (Example 101).

16.1mg(70%)

Example 49

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]methionine (Example 102).

11.7mg(52%)

Example 50

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]methionine (Example 103).

13.2mg(58.6%)

Example 51

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]phenylalanine (Example 104).

9.7mg(41.9%)

Example 52

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]phenylalanine (Example 105).

12.2mg(52.9%)

Example 53

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]cyclohexylalanine (Example 106).

10.1mg(43.7%)

Example 54

L-N-ε-(Benzyloxycarbonyl),
N-α-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]lysine

10mg(36%)

Example 55

D-N-ε-(Benzyloxycarbonyl),
N-α-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]lysine

24.4mg(88%)

Example 56

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoylphenyl acylsulphonamide

(a) 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (222 mg, 0.5 mmol), 1-[3-(dimethylamino)propyl]-3-ethyl-carbodiimide (100 mg, 0.525 mmol), 4-dimethylaminopyridine (63 mg, 0.525 mmol), benzenesulphonamide (82 mg, 0.525 mmol) and 5 ml of dichloromethane was stirred at room temperature for 4 days. The reaction mixture

was diluted with dichloromethane, washed subsequently with 1M hydrochloric acid, water and a saturated solution of sodium chloride. Toluene was added to the organic phase and the combined phases were concentrated. The residue was purified by chromatotron (silica gel, ethyl acetate). This gave 106 mg (0.182 mmol, 36%) of 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoylphenyl acylsulphonamide.
(b) A stirred solution of 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoylphenyl acyl sulphonamide (57 mg, 0.1 mmol) in 2 ml of dichloromethane was kept under nitrogen and cooled to-400C. To the solution was added 0.2 ml of 1M boron tribromide (0.2 mmol, solution in dichloromethane). After 48 hours at room temperature the reaction mixture was treated with cold 1 M hydrochloric acid, the phases were separated and the organic phase was washed once with water. The organic phase was dried over magnesium sulphate, filtered and concentrated. The residue was purified by chromatotron (silica gel, 9:1:0.1 chloroform/ methanol/acetic acid) to give 44 mg (80%) of 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl phenyl acylsulphonamide as a white solid.

Example 57

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoylmethyl acylsulphonamide

(a) 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (222 mg, 0.5 mmol), was coupled with methylsulphonamide (48 mg, 0.525 mmol) using the method described in Example 56(a). The reaction mixture was stirred for two weeks. The residue was purified by chromatotron (silica gel, ethyl acetate) to give 147 mg (56%) of 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoylmethyl acylsulphonamide.
(b) The above methoxy compound was demethylated using the method described in Example 56(b). The residue was purified by chromatotron (silica gel, 9:1:0.1 chloroform/ methanol/acetic acid) to give 51 mg (35%) of 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl methylsulphonamide as a white solid.

Example 58

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-5-hydroxy-1-naphthalenesulphonamide

To a stirred mixture of 5-hydroxy-1-naphthalenesulphonamide (0.175 mmol) in dichloromethane (0.2 ml) was added a solution of 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoic acid (0.035 mmol), DIEA (0.175 mmol) and dichloromethane (0.2 ml). dimethyl formamide was added to the solution if the

sulphonamide not dissolved completely in dichloromethane. After 15 minutes PyBOP (0.042 mmol) and HOBt (0.001 mmol) in dichloromethane (0.3 ml) was added. The reaction mixture was heated at 50°C for 20 hours. After cooling to room temperature, dichloromethane (1 ml) and citric acid solution (5%, 1ml) was added and stirred vigorously for 30 min. The organic phase was dried, concentrated and the residue was finally subjected to semi-preparative HPLC (Silica column: 250x20mm, ethyl acetate/n-heptane (both with 0.5% acetic acid). Gradient: first 2min 15% ethyl acetate, then over 13min to 100% ethyl acetate, then additional 5 min 100% ethyl acetate) to give 12 mg (54 %) of the title compound.

Example 59

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-toluenesulphonamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (0.035 mmol) was coupled with toluenesulphonamide (0.175 mmol) using the method described in Example 58. Purification on HPLC of the residue gave 14 mg (69 %) of the title compound.

Example 60

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-nitrobenzenesulphonamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (. 0.035 mmol) was coupled with 4-nitrophenylsulfonamid (0.175 mmol) using the method described in Example 58. Purification on HPLC of the residue gave 8 mg (37 %) of the title compound.

Example 61

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl sulfamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (0.035 mmol) was coupled with sulfamide (0.175 mmol) using the method described in Example 58. Purification on HPLC of the residue gave 13 mg (73 %) of the title compound.

Example 62

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-5-dimethylamino-1-naphthalenesulphonamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (, 0.035 mmol) was coupled with 5-dimethylamino-1-naphthalenesulphonamide (0.175 mmol) using the method described in Example 58. Purification on HPLC of the residue gave 8 mg (34 %) of the title compound.

Example 63

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-aminobenzenesulphonamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (0.035 mmol) was coupled with 4-aminobenzenesulphonamide (0.175 mmol) using the method described in Example 58. Purification on HPLC of the residue gave 7 mg (34 %) of the title compound.

Example 64

Methyl-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-2-sulphonamide] benzoate

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (0.035 mmol) was coupled with methyl 2-sulphonamide benzoate (0.175 mmol) using the method described in Example 58. Purification on HPLC of the residue gave 12 mg (55 %) of the title compound.

Example 65

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-2-aminobenzenesulphonamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (0.035 mmol) was coupled with 2-aminobenzenesulphonamide (0.175 mmol) using the method described in Example 58. Purification on HPLC of the residue gave 11 mg (54 %) of the title compound.

Example 66

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-2-toluenesulphonamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (0.035 mmol) was coupled with 2-toluenesulphonamide (0.175 mmol) using the method described in Example 58. Purification on HPLC of the residue gave 15 mg (74 %) of the title compound.

Example 67

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-(2-aminoethyl)benzenesulphonamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (0.035 mmol) was coupled with 4-(2-aminoethyl)benzenesulphonamide (0.175 mmol) using the method described in Example 58. Purification on HPLC of the residue gave 10 mg (47 %) of the title compound.

Example 68

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-(2-aminomethyl)benzenesulphonamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (, 0.035 mmol) was coupled with 4-(2-aminomethyl)benzenesulphonamide (0.175 mmol) using the method described in Example 58. Purification on HPLC of the residue gave 16 mg (76 %) of the title compound.

Example 69

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-3-nitrobenzenesulphonamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (0.035 mmol) was coupled with 3-nitrobenzenesulphonamide (0.175 mmol) using the method described in Example 58. Purification on HPLC of the residue gave 7 mg (33 %) of the title compound.

Example 70

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-chlorobenzenesulphonamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (0.035 mmol) was coupled with 4-chlorobenzenesulphonamide (0.175 mmol) using the method described in Example 58. Purification on HPLC of the residue gave 13 mg (62 %) of the title compound.

Example 71

D-Dimethyl N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartate.

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (250 mg) was coupled with *D*-dimethyl aspartate hydrochloride (135 mg) using the method described in Example 20(a) to give 230 mg (74%) of *D*-dimethyl N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartate. MS (M-H, electrospray): m/z$^+$ 586.

Example 72

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartic acid

D-Dimethyl N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartate (Example 41, 110 mg) was hydrolyzed using the method described in Example 23 to give 80 mg (77%) of *D*-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartic acid. MS (M-H, electrospray): m/z$^+$ 558.

Example 73

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]imino diacetic acid

(a) 3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (900 mg), dimethyl imino diacetate (500 mg) and EDCI (470 mg) in 10 ml of dimethyl formamide was stirred at room temperature overnight. The mixture was diluted with ethyl acetate and then washed with sodium bicarbonate (1 M), 1 M hydrochloric acid, and brine, dried, filtered and concentrated. The residue was purified on a silica column eluted with ethyl acetate/petroleum ether (1:2) affording 720 mg (63%) of dimethyl N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]imino diacetate.
(b) The above ester was hydrolyzed as described in Example 23 to give 700 mg (93%) of N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]imino diacetic acid

Example 74

L-N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartic acid.

(a) A solution of 3,5-dichloro-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (50 mg), 3-ethyl-1-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI), (30 mg), 1-hydroxybenzotriazole hydrate (HBT), (28 mg) in dimethyl formamide (1 ml) was stirred at room temperature for 0.5 h followed by addition of a solution of *L*-di-*t*-butyl aspartate hydrochloride (52 mg) and triethylamine (32 mg) in dimethyl formamide (1 ml). After stirring for three days, the mixture was partitioned between water and ethyl acetate. The organic phase was washed with brine and then dried, filtered and concentrated. The residue was chromatographed on silica gel eluted with ethyl acetate/light petroleum ether (1:4). Pure fractions were pooled and concentrated to give *L*-di-*t*-butyl N-[3,5-dichloro-4 (4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartate (68 mg, 83%).

(b) The above ester (48 mg) was hydrolyzed using the method described in Example 23 to give *L*-N-[3,5-dichloro-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartic acid (27 mg, 70%).

Example 75

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionyl amide

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionic acid (400 mg) was refluxed overnight in thionyl chloride (5 ml). The reaction mixture was concentrated and the residue dissolved in dichloromethane. Ammonia was bubbled into the solution. Concentration and recrystallization from ethyl acetate-petroleum ether gave 330 mg (83%) of 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionyl amide.

Example 76

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionylimino diacetic acid

a) A mixture of 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionic acid (700 mg), dimethyl iminodiacetate (320 mg) and EDCI (330mg) in 20 ml of dichloromethane was stirred at room temperature overnight. The mixture was diluted with dichloromethane and then washed with sodium bicarbonate (1 M), 1 M hydrochloric acid, and brine, dried, filtered and concentrated. The residue was purified on a silica column eluted with ethyl acetate/petroleum ether (1:2) affording 750 mg (83%) of dimethyl N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionyl]imino diacetate.

b) The above ester (750 mg) was hydrolyzed using the method described in Example 23 to give 700 mg (81%) of N-[3,5-Dibromo-4-(4-hydroxy-3-isopropyl-phenoxy)phenylpropionyl]imino diacetic acid.

Example 77

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionyl]imino diacetic acid monobutylamide

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionyl]imino diacetic acid (Example 76, 500 mg), was coupled with n-butylamine(63 mg) in dimethyl formamide using the method described in Example 46 (a). The crude residue was purified on a silica column eluted with chlorform/methanol 9:1to give 300mg (55%) of N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionyl]imino diacetic acid monobutylamide

Example 78

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionyl]imino diacetic acid monoaniline

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionyl]imino diacetic acid (Example 76, 500 mg), was coupled with aniline using the method described in

Example 76(a). The crude residue was purified on a silica column eluted with chlorform/methanol 9:1to give 90 mg (80%) of N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionyl]imino diacetic acid monoaniline.

Example 79

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionyl]imino diacetic acid dianiline

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionyl]-imino diacetic acid (Example 76, 172 mg), was coupled with aniline using the method described in Example 76(a). The crude residue was purified on a silica column eluted with chlorform/methanol 9:1to give 170 mg (80%) of N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionyl]imino diaceticacid dianiline.

Example 80

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionyl]alanine

a) 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionic acid (90 mg) was coupled to *L*-alanine methyl ester hydrochloride (29mg) using the method described in Example 20 to give100mg (93%) of *L*-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionyl]alanine methyl ester.

b) The above ester (80 mg) was hydrolyzed using the method described in Example 23 to give 70 mg (90%) of *L*-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionyl]alanine.

Example 81

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartic acid

a) 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionic acid (460mg) was coupled to *L*-di-*t*-butyl aspartate hydrochloride (280mg) using the method described in Example 20 to give 630mg (92%) of *L*-di-*t*-butyl N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropiono] aspartate.

b) The above ester (600mg) was hydrolyzed using the method described in Example 23 to give 500 mg (79%) of *L*-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]-aspartic acid.

Example 82

Methyl *L*-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionyl]aspartate

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenypropionyl]aspartic acid (Example 81, 110mg) was esterified using the method described in Example 20 to give 110mg 95%) of Methyl L-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionyl]aspartate.

Example 83

Methyl *D*-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionyl]aspartate.

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionic acid (230mg) was coupled with D-di-methyl aspartate hydrochloride (280mg) using the method described in Example 20 to give 300mg (80%) of D-dimethyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionyl]aspartate.

Example 84

Methyl *D*-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartate.

Methyl *D*-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartat (300mg) was hydrolysed using the method described in Example 23 to give 280 mg (79%) of *D*-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartic acid.

Example 85

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionyl benzenesulphonamide

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionic acid (140 mg), benzenesulphonamide (50 mg) EDCI (60 mg) 4-DMAP (45 mg) in dichloromethane , gave 40 mg (20%) of 3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionyl benzenesulphonamide.

Example 86

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylbutyl]methansulphonylamide.

a) Sodium boro hydride (230 mg) was added to a solution of methyl 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)phenylpropionate (1.4 g) in ethanol. The mixture was refluxed for 4 hours to give 1.1 g of 3,5-dibromo-4-(4methoxy-3-isopropylphenoxy)phenylpropionol (80%).

b) The above alcohol (460 mg), carbon tetrabromide (340 mg) and triphenylphosphine (262mg) in acetonitrile was stirred overnight, to give 460 mg 3,5-dibromo-4-(4methoxy-3-isopropylphenoxy)phenylpropylbromide (88%).

c) The above bromide (500 mg) and sodium cyanide (100 mg) in dimethyl formamide-water (1:1), was stirred at 90°C for two hours to give 450 mg 3,5-dibromo-4-(4methoxy-3-isopropylphenoxy)phenylpropylnitril (96%).

d) A solution of the above propionylnitrile (230 mg) and sodium borohyride (70 mg) in tetrahydrofuran was treated with boron trifluoride ether complex (140 mg) at room temperature, and stirred overnight. affording 200 mg 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)phenylbutylamine (85%).

e) A solution of above butylamine(100 mg) and triethylamine (20 mg) in dichloromethan were treated with methansulfonyl chloride (23 mg) at 0°C, then stirred at room temperature for one hour affording 100 mg N-[3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)phenylbutyl]methansulfurnylamide.(90%)

f) The above amide(100mg) was demethylated with boron tribromide as described in Example 2(b). The crude product was recrystallized from dichloromethane and light petroleum ether to give 80 mg of N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylbutyl]methansulfurnylamide.

Example 87

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylethyl tetrazole.

a) A mixture of 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)phenylpropionitrile. (210 mg), sodium azide (200 mg) and ammonium chloride (160 mg) in dimethyl formamide was refluxed overnight. The mixture was partitioned between 1 M hydrochloric acid and ethyl acetate. The organic phase was concentrated and the residue was purified by column chromatography on a silica column eluted with chloroform and methanol (9:1) to give 50 mg (20%) of 5-[3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)phenylethyl]tetrazole.

(b) The above methoxy compound (50 mg) was demethylated using the method described in Example 2(b) to give 49 mg (90%) of 5-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylethyl]tetrazole.

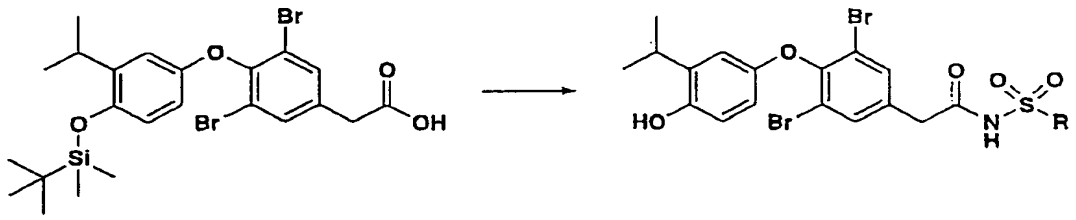
Example 88

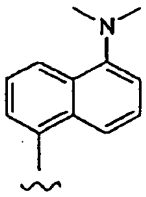
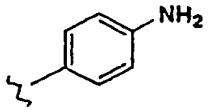
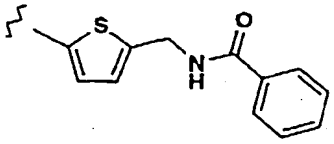
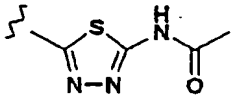
3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl-5-dimethylamino-1-naphthalen esulphonamide

To a solution of the 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (50 mg, 0.09 mmol), dimethylaminopyridine (4 mg, 0.018 mmol) and 5-dimethylamino-1-naphthalenesulphonamide (45 mg, 0.18 mmol) in 50% dichloromethane in dimethyl formamide (0.2 ml) was added a solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (28 mg, 0.13 mmol) and diisopropylethyl amine (17 mg, 0.13 mmol) in 50% methylene chloride in dimethyl formamide (0.2 ml). The reaction mixture was vortexed and allowed to stand at room temperature for 6 hours. A solution of ammonium fluoride (0.5 M in methanol; 0.4 ml) was added. After 16 h, the reaction mixture was evaporated to dryness, re-dissolved in a solvent mixture containing 90% methanol, 10% water and 0.1% trifluoroacetic acid (2 ml) and purified by preparative HPLC (YMC S5 ODS 30 x 250 mm: 50-100% solvent B in 30 min: solvent A - 90% water, 10% methanol, 0.1% trifluoroacetic acid; solvent B – 10% water, 90% methanol, 0.1% trifluoroacetic acid: flow rate 25 ml per min: detection 220 nm). The yield was 10.1 mg (16%).

Example 89-91

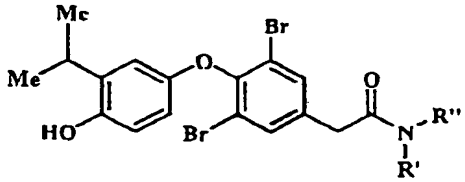
These compounds were prepared and purified in a similar manner as above. For a table of Examples 88-90 comprising the coupled sulphonamide, retention times and mass spectra, se Scheme below.



Example	R group	MS (ESI+)	R_t (min)†
88		677	6.9
89		598	4.3
90		722	5.1
91		648	4.9

YMC ODS 4.6 x 50 mm: 50-100% solvent B in 8 min: solvent A - 90% water, 10% methanol, 0.2% phosphoric acid; solvent B – 10% water, 90% methanol. 0.2% phosphoric acid: flow rate 2.5 ml per min: detection 220 nm

Examples 92-191



Procedures for the synthesis of the library compounds indicated in the Table below are described in Lawrence, R.M.; Biller, S.A.; Fryszman, O.M.; Poss, M.A. *Synthesis* **1997**, 553.

[1]HPLC retention time in minutes and gradient method. Reverse phase HPLC analyses performed on YMC S5 ODS 4.6 x 50 mm analytical columns, detection at 220 nm, and 4 minute gradient elutions by either: method a, 0% B, 100% A to 100% B, 0% A; or method b, 20% B, 80% A to 100% B, 0% A, where solvent A is 90% water, 10% methanol, 0.2% phosphoric acid and solvent B is 10% water, 90% methanol, 0.2% phosphoric acid.
[2]MS result obtained on a Micromass Platform II using electrospray, both positive and negative ion modes.
[3]Method A examples were prepared by synthesis procedure A in the reference cited above. In these examples, a second basic nitrogen is present in the amine coupling partner. However, only one nitrogen is capable of giving the normal acylation product. Method B examples were prepared by procedure C in the reference cited above.

Example	-NR'R"	HPLC[1]	MS[2]	Formula	Method[3]
92	3-(AMINOMETHYL)PYRIDINE	2.76,a	m/z 534.84 (M+H)	C23H22Br2N2O3	A
93	2-(2-AMINOETHYL)PYRIDINE	2.73,a	m/z 548.83 (M+H)	C24H24Br2N2O3	A
94	3-(2-AMINOETHYL)PYRIDINE	2.73,a	m/z 548.82 (M+H)	C24H24Br2N2O3	A
95	2-(AMINOMETHYL)PYRIDINE	2.84,a	m/z 534.85 (M+H)	C24H30Br2N2O3	A
96	4-(AMINOMETHYL)PYRIDINE	2.74,a	m/z 534.82 (M+H)	C24H30Br2N2O3	A
97	1-(4-METHOXYPHENYL)PIPERAZINE DIHYDROCHLORIDE	3.33,a	m/z 618.81 (M+H)	C29H32Br2N2O3	A
98	1-(2-FLUOROPHENYL)PIPERAZINE	3.53,a	m/z 607.16 (M+H)	C34H32Br2N2O3	A
99	2-(2-(AMINOMETHYL)PHENYLTHIO)BENZYL ALCOHOL	4.42,a	m/z 671.97 (M+H)	C31H29Br2NO4S	B
100	2-(1-CYCLOHEXENYL)ETHYLAMINE	4.56,a	m/z 551.98 (M+H)	C25H29Br2NO3	B
101	2-AMINOINDAN	4.44,a	m/z 559.88 (M+H)	C26H25Br2NO3	B
102	2-AMINOMETHYLBENZODIOXAN	4.39,a	m/z 591.93 (M+H)	C26H25Br2NO5	B
103	3-PHENYL-1-PROPYLAMINE	4.44,a	m/z 560.00 (M-H)	C26H27Br2NO3	B
104	2-(P-TOLYL)ETHYLAMINE	4.48,a	m/z 559.95 (M-H)	C26H27Br2NO3	B
105	1-(3-AMINOPROPYL)-2-PYRROLIDINONE	3.97,a	m/z 568.97 (M+H)	C24H28Br2N2O4	B
106	BETA-ALANINE 4-METHOXY-BETA-NAPHTHYLAMIDE	4.52,a	m/z 670.88 (M+H)	C31H30Br2N2O5	B
107	2-CHLOROBENZYLAMINE	4.38,a	m/z 612.98 (M+?)	C24H22Br2ClNO3	B
108	2-AMINOMETHYL-3-CHLORODIPHENYLETHER	4.65,a	m/z 660.08 (M+H)	C30H26Br2ClNO4	B
109	DL-ALPHA-AMINO-EPSILON-CAPROLACTAM	4.03,a	m/z 554.86 (M+H)	C23H26Br2N2O4	B
110	L-PHENYLALANINOL	4.22,a	m/z 577.92 (M+H)	C26H27Br2NO4	B
111	4-(1,2,3-THIADIAZOL-4-YL	4.21,a	m/z 617.69	C26H23Br2N3O3S	B

Example	-NR'R"	HPLC[1]	MS[2]	Formula	Method[3]
	)BENZYLAMINE		(M+H)		
112	2-AMINOMETHYLTHIOPHENE	4.21,a	m/z 539.84 (M+H)	C22H21Br2NO3S	B
113	1-(1-NAPHTHYL)ETHYLAMINE	4.54,a	m/z 597.83 (M+H)	C29H27Br2NO3	B
114	3-CHLORO-4-METHYL BENZYLAMINE	4.53,a	m/z 581.80 (M+H)	C25H24Br2ClNO3	B
115	TETRAHYDROFURFURYLAMINE	4.07,a	m/z 527.90 (M+H)	C22H25Br2NO4	B
116	2,4-DICHLOROPHENETHYLAMINE	4.66,a	m/z 615.73 (M+H)	C25H23Br2Cl2NO3	B
117	ETHYL 4-AMINO-1-PIPERIDINECARBOXYLATE	4.21,a	m/z 599.05 (M+H)	C25H30Br2N2O5	B
118	2,6-DIFLUOROBENZYLAMINE	4.25,a	m/z 569.82 (M+H)	C24H21Br2F2NO3	B
119	2-IODOBENZYLAMINE	4.46,a	m/z 659.45 (M+H)	C24H22Br2INO3	B
120	2-METHYLBENZYLAMINE	4.38,a	m/z 547.89 (M+H)	C25H25Br2NO3	B
121	BENZYLAMINE	4.27,a	m/z 533.85 (M+H)	C24H23Br2NO3	B
122	3-METHYLBENZYLAMINE	4.38,a	m/z 547.89 (M+H)	C25H25Br2NO3	B
123	2-METHOXYPHENETHYLAMINE	4.41,a	m/z 577.81 (M+H)	C26H27Br2NO4	B
124	3-METHOXYPHENETHYLAMINE	4.35,a	m/z 577.87 (M+H)	C26H27Br2NO4	B
125	2-ETHOXYBENZYLAMINE	4.42,a	m/z 577.86 (M+H)	C26H27Br2NO4	B
126	(R)-(-)-1-CYCLO-HEXYLETHYLAMINE	4.56,a	m/z 553.90 (M+H)	C25H31Br2NO3	B
127	4-METHOXYPHENETHYLAMINE	4.32,a	m/z 577.83 (M+H)	C26H27Br2NO4	B
128	2-FLUOROBENZYLAMINE	4.27,a	m/z 551.85 (M+H)	C24H22Br2FNO3	B
129	2-CHLORO-6-METHYLBENZYLAMINE	4.48,a	m/z 581.85 (M+H)	C25H24Br2ClNO3	B
130	4-CHLOROBENZYLAMINE	4.42,a	m/z 567.83 (M+H)	C24H22Br2ClNO3	B
131	BETA-METHYLPHENETHYLAMINE	4.43,a	m/z 561.88 (M+H)	C26H27Br2NO3	B
132	1,1-DI(P-ANISYL)METHYLAMINE	4.47,a	m/z 669.88 (M+H)	C32H31Br2NO5	B
133	MAYBRIDGE BTB 12133	4.18,a	m/z 623.84 (M+H)	C27H29Br2NO6	B
134	DL-2-AMINO-1-PENTANOL	4.12,a	m/z 529.91 (M+H)	C22H27Br2NO4	B
135	L-PHENYLALANINE-P-NITROANILIDE	4.56,a	m/z 711.88 (M+H)	C32H29Br2N3O6	B
136	ETHYL 3-AMINOBUTYRATE	4.16,a	m/z 557.85 (M+H)	C23H27Br2NO5	B
137	(1S,2R)-(+)-2-AMINO-1,2-DIPHENYLETHANOL	4.28,a	m/z 639.92 (M+H)	C31H29Br2NO4	B
138	2-FLUOROPHENETHYLA	4.37,a	m/z 565.90	C25H24Br2FNO3	B

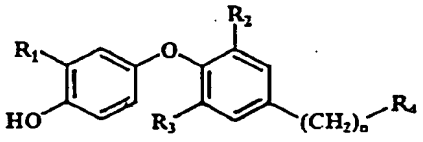
Example	-NR'R"	HPLC[1]	MS[2]	Formula	Method[3]
	MINE		(M+H)		
139	2-ETHYLHEXYLAMINE	4.70,a	m/z 555.93 (M+H)	C25H33Br2NO3	B
140	3-FLUOROPHENETHYLAMINE	4.36,a	m/z 565.85 (M+H)	C25H24Br2FNO3	B
141	(1S,2S)-(+)-2-AMINO-3-METHOXY-1-PHENYL-1-PROPANOL	4.19,a	m/z 607.89 (M+H)	C27H29Br2NO5	B
142	NONYLAMINE	4.88,a	m/z 569.95 (M+H)	C26H35Br2NO3	B
143	2,5-DICHLOROBENZYLAMINE	4.49,a	m/z 601.72 (M+H)	C24H21Br2Cl2NO3	B
144	2-METHYLCYCLOHEXYLAMINE	4.44,a	m/z 539.91 (M+H)	C24H29Br2NO3	B
145	3-METHYLCYCLOHEXYLAMINE	4.51,a	m/z 539.90 (M+H)	C24H29Br2NO3	B
146	3-N-PROPOXYPROPYLAMINE	4.30,a	m/z 543.90 (M+H)	C23H29Br2NO4	B
147	2,3-DIMETHYLBENZYLAMINE	4.48,a	m/z 561.91 (M+H)	C26H27Br2NO3	B
148	3-CHLOROBENZYLAMINE	4.40,a	m/z 567.79 (M+H)	C24H22Br2ClNO3	B
149	4-TERT-BUTYLCYCLOHEXYLAMINE	4.80,a	m/z 581.97 (M+H)	C27H35Br2NO3	B
150	(1S,2S)-(+)-THIOMICAMINE	3.94,a	m/z 639.80 (M+H)	C27H29Br2NO5S	B
151	2,4-DIMETHYLBENZYLAMINE	4.49,a	m/z 561.89 (M+H)	C26H27Br2NO3	B
152	2-AMINOETHYL PHENYL SULFIDE	4.44,a	m/z 579.83 (M+H)	C25H25Br2NO3S	B
153	PHENETHYLAMINE	4.36,a	m/z 547.87 (M+H)	C25H25Br2NO3	B
154	TYRAMINE	4.04,a	m/z 563.86 (M+H)	C25H25Br2NO4	B
155	L-TYROSINE METHYL ESTER	4.01,a	m/z 621.97 (M+H)	C27H27Br2NO6	B
156	BENZHYDRYLAMINE	4.52,a	m/z 609.82 (M+H)	C30H27Br2NO3	B
157	4-METHOXYBENZYLAMINE	4.25,a	m/z 563.85 (M+H)	C25H25Br2NO4	B
158	2,3-DICHLOROBENZYLAMINE	4.52,a	m/z 601.71 (M+H)	C24H21Br2Cl2NO3	B
159	GLYCINE N-BUTYL ESTER HYDROCHLORIDE	4.03,b	m/z 557.85 (M+H)	C23H27Br2NO5	B
160	D-(-)-ALPHA-PHENYLGLYCINE ETHYL ESTER HYDROCHLORIDE	4.11,b	m/z 605.84 (M+H)	C27H27Br2NO5	B
161	4-CHLORO-2-FLUOROBENZYLAMINE HYDROCHLORIDE	4.27,b	m/z 585.80 (M+H)	C24H21Br2ClFNO3	B
162	TRANS-2-PHENYLCYCLOPROPYLAMINE HYDROCHLORIDE	4.22,b	m/z 559.86 (M+H)	C26H25Br2NO3	B
163	ETHYL	3.87,b	m/z 557.85 (M+H)	C23H27Br2NO5	B

Example	-NR'R"	HPLC[1]	MS[2]	Formula	Method[3]
	4-AMINOBUTYRATE HYDROCHLORIDE				
164	DL-HOMOCYSTEINE THIOLACTONE HYDROCHLORIDE	3.65,b	m/z 543.80 (M+H)	C21H21Br2NO4S	B
165	4-NITROBENZYLAMINE HYDROCHLORIDE	3.99,b	m/z 578.85 (M+H)	C24H22Br2N2O5	B
166	NORPHENYLEPHRINE HYDROCHLORIDE	3.60,b	m/z 579.84 (M+H)	C25H25Br2NO5	B
167	GLYCINE ETHYL ESTER HYDROCHLORIDE	3.71,b	m/z 529.87 (M+H)	C21H23Br2NO5	B
168	DL-ALANINE ETHYL ESTER HYDROCHLORIDE	3.83,b	m/z 543.86 (M+H)	C22H25Br2NO5	B
169	SARCOSINE ETHYL ESTER HYDROCHLORIDE	3.79,b	m/z 543.92 (M+H)	C22H25Br2NO5	B
170	4-NITRO-N-PROPYLBENZYLAMINE HYDROCHLORIDE	4.29,b	m/z 620.89 (M+H)	C27H28Br2N2O5	B
171	PIPERIDINE	3.98,b	m/z 511.93 (M+H)	C22H25Br2NO3	B
172	3-METHYLPIPERIDINE	4.14,b	m/z 525.91 (M+H)	C23H27Br2NO3	B
173	3-(HYDROXYMETHYL)-PIPERIDINE	3.66,b	m/z 541.89 (M+H)	C23H27Br2NO4	B
174	1,2,3,4-TETRAHYDROISOQUINOLINE	4.23,b	m/z 559.85 (M+H)	C26H25Br2NO3	B
175	2-ETHYLPIPERIDINE	4.25,b	m/z 539.90 (M+H)	C24H29Br2NO3	B
176	3,4-DICHLORO-N-ETHYL BENZYLAMINE	4.54,b	m/z 629.75 (M+H)	C26H25Br2Cl2NO3	B
177	2-METHYLPYRROLIDINE	3.99,b	m/z 511.90 (M+H)	C22H25Br2NO3	B
178	N-ETHYL-N-PROPYLAMINE	4.11,b	m/z 513.89 (M+H)	C22H27Br2NO3	B
179	4-METHYLPIPERIDINE	4.15,b	m/z 525.91 (M+H)	C23H27Br2NO3	B
180	(S)-(+)-2-(METHOXYMETHYL)PYRROLIDINE	3.99,b	m/z 541.90 (M+H)	C23H27Br2NO4	B
181	N-BENZYLETHANOLAMINE	4.01,b	m/z 577.86 (M+H)	C26H27Br2NO4	B
182	DIBENZYLAMINE	4.56,b	m/z 623.79 (M+H)	C31H29Br2NO3	B
183	4-BENZYL-4-HYDROXYPIPERIDINE	4.12,b	m/z 617.88 (M+H)	C29H31Br2NO4	B
184	(R)(-)-2-BENZYLAMINO-1-BUTANOL	4.16,b	m/z 605.83 (M+H)	C28H31Br2NO4	B
185	N-(N-ETHYLAMINOACETYL)-2,6-DIMETHYLANILINE	4.00,b	m/z 632.69 (M+H)	C29H32Br2N2O4	B
186	N-ETHYL-O-METHOXYBENZYLAMINE	4.35,b	m/z 591.93 (M+H)	C27H29Br2NO4	B
187	MAYBRIDGE NRB 01961	4.40,b	m/z 647.88 (M+H)	C30H33Br2NO5	B
188	2-((N-ETHYLAMINO)METHYL)-4-NITROPHENOL	4.05,b	m/z 622.80 (M+H)	C26H26Br2N2O6	B

Example	-NR'R''	HPLC[1]	MS[2]	Formula	Method[3]
189	MAYBRIDGE SEW 01484	4.48,b	m/z 671.89 (M+H)	C31H29Br2NO4S	B
190	3-AZABICYCLO-[3.2.2]NONANE	4.28,b	m/z 551.89 (M+H)	C25H29Br2NO3	B
191	N-(2-METHOXY-ETHYL)ETHYLAMINE	3.89,b	m/z 529.88 (M+H)	C22H27Br2NO4	B

What is claimed is:

1. A compound having the formula



wherein

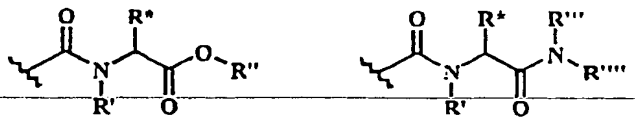
n is an integer from 0 to 4

R_1 is alkyl of 1 to 6 carbons or cycloalkyl of 3 to 7 carbons;

R_2 and R_3 are the same or different and are hydrogen, halogen, alkyl of 1 to 4 carbons, at least one of R_2 and R_3 being other than hydrogen;

R_4 is a heteroaromatic moiety which may be substituted or unsubstituted and is linked to $(CH_2)_n$ via a nitrogen atom or, in the case of a tetrazole moiety, linked to $(CH_2)_n$ either via nitrogen or carbon, an amine (NR'R"); a carboxylic acid amide (CONR'R") or a acylsulphonamide ($CONHSO_2R'$) derivative, or a pharmaceutically acceptable salt thereof, and all stereoisomers thereof.

2. The compound as defined in Claim 1 where the amine portion of the amide can be derived from an L or a D alpha amino acid such that the general structure -CONR'R" can be represented by



and R', R", R''' and R'''' are the same or different and are independently selected from hydrogen, alkyl, aryl and heteroaryl, substituted or unsubstituted, and R* may be hydrogen, alkyl, aryl and heteroaryl, substituted and unsubstituted, and may also be any of the side chains found in the naturally occuring alpha-amino acids.

3. The compound as defined in Claim 1 where n is 0 or 1 or 2.

4. The compound as defined in Claim 1 wherein R_2 and R_3 are each independently halogen.

5. The compound as defined in Claim 1 wherein R_2 and R_3 are each independently an alkyl group.

6. The compound as defined in Claim 1 wherein one of R_2 and R_3 is halogen and the other is an alkyl group.

7. The compound as defined in Claim 1 wherein one of R_2 and R_3 is halogen and the other is hydrogen.

8. The compound as defined in Claim 1 wherein one of R_2 and R_3 is alkyl and the other is hydrogen.

9. The compound as defined in Claim 1 wherein R_2 and R_3 are independently Cl, Br, methyl or ethyl.

10. The compound as defined in Claim 1 wherein R_1 is isopropyl.

11. The compound as defined in Claim 1 wherein R_4 is heteroaromatic hydrocarbon, carboxylic acid amide, or an acylsulphonamide.

12. The compound as defined in Claim 1 which is
L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]aspartic acid.,
N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-4-hydroxyaniline,
N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]phthalimide,
N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]hydantoin,
N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]pyrazole,
N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]imidazole,
N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]4-azabenzimidazole,

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-4-imidazole carboxylic acid,

1-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-4-methyl-5-imidazole carboxylic acid,

Ethyl 1-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-4-pyrazole carboxylate,

1-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-4-pyrazole carboxylic acid,

Ethyl 1-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-3-trifluoromethyl)pyrazole-4 carboxylate,

1-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-3-trifluoromethyl)pyrazole-4 carboxylic acid,

1-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-(3-methyl)pyrazole-5-carboxylic acid,

1-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-5-azabenzimidazole,

1-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-6-azabenzimidazole,

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyltetrazole,

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl(1-methyl)tetrazole and 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl(2-methyl)tetrazole,

3,5-Dimethyl-4-(4-hydroxy-3-isopropylphenoxy)benzyltetrazole,

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]aspartic acid,

L-Dimethyl N-[3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoyl] aspartate,

D-Dimethyl N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]aspartate,

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]aspartic acid,

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]glutamic acid,

L-Dimethyl N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]glutamate,

3-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]aminobenzoic acid,

4-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]aminobenzoic acid,

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]alanine,

L-2-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]amino-1,4-butanediol,

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]valine

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]leucine

L-S-Benzyl, N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]cysteine

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]tyrosine

L-N-δ-(2,2,5,7,8-Pentamethylchroman-6-sulfonyl), N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]arginine

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]aminobutyric acid

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-2-toluenesulphonamide

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-(2-aminoethyl)benzene-sulphonamide

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-(2-aminomethyl)benzene-sulphonamide

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-3-nitrobenzenesulphonamide

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-chlorobenzene-sulphonamide

D-Dimethyl N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartate

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartic acid

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]imino diacetic acid

L-N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartic acid

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionyl amide

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionylimino diacetic acid

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionyl]imino diacetic acid monobutylamide

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionyl]imino diacetic acid monoaniline

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionyl]imino diacetic acid dianiline

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionyl]alanine

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartic acid

Methyl *L*-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionyl]aspartate

Methyl *D*-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartate

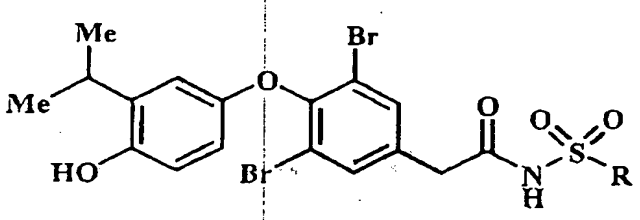
Methyl *D*-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionyl] aspartate

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylpropionyl benzenesulphonamide

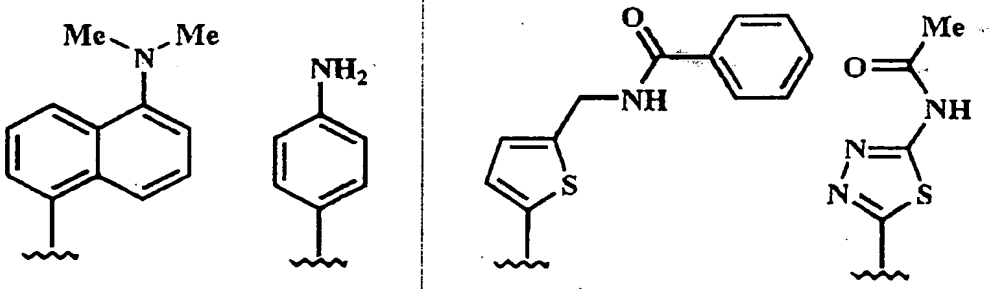
N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylbutyl]methan-sulphonylamide

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylethyl tetrazole

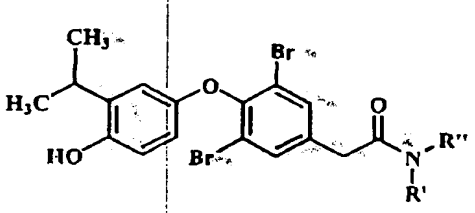
and the compounds shown below,



R=



and the compounds indicated in the table below.



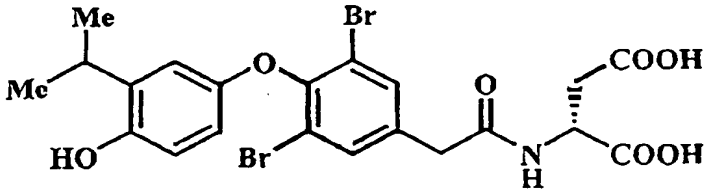
-NR'R"	Formula
3-(AMINOMETHYL)PYRIDINE	C23H22Br2N2O3
2-(2-AMINOETHYL)PYRIDINE	C24H24Br2N2O3
3-(2-AMINOETHYL)PYRIDINE	C24H24Br2N2O3
2-(AMINOMETHYL)PYRIDINE	C24H30Br2N2O3
4-(AMINOMETHYL)PYRIDINE	C24H30Br2N2O3
1-(4-METHOXYPHENYL)PIPERAZINE DIHYDROCHLORIDE	C29H32Br2N2O3
1-(2-FLUOROPHENYL)PIPERAZINE	C34H32Br2N2O3
2-(2-(AMINOMETHYL)PHENYLTHIO)BENZYL ALCOHOL	C31H29Br2NO4S
2-(1-CYCLOHEXENYL)ETHYLAMINE	C25H29Br2NO3
2-AMINOINDAN	C26H25Br2NO3
2-AMINOMETHYLBENZODIOXAN	C26H25Br2NO5
3-PHENYL-1-PROPYLAMINE	C26H27Br2NO3
2-(P-TOLYL)ETHYLAMINE	C26H27Br2NO3
1-(3-AMINOPROPYL)-2-PYRROLIDINONE	C24H28Br2N2O4

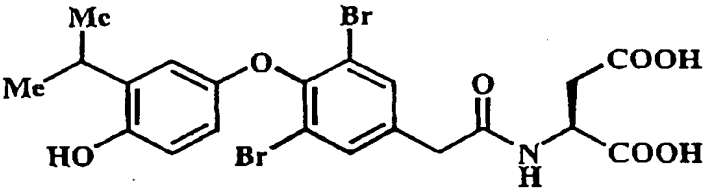
-NR'R"	Formula
BETA-ALANINE 4-METHOXY-BETA-NAPHTHYLAMIDE	C31H30Br2N2O5
2-CHLOROBENZYLAMINE	C24H22Br2ClNO3
2-AMINOMETHYL-3-CHLORODIPHENYLETHER	C30H26Br2ClNO4
DL-ALPHA-AMINO-EPSILON-CAPROLACTAM	C23H26Br2N2O4
L-PHENYLALANINOL	C26H27Br2NO4
4-(1,2,3-THIADIAZOL-4-YL)BENZYLAMINE	C26H23Br2N3O3S
2-AMINOMETHYLTHIOPHENE	C22H21Br2NO3S
1-(1-NAPHTHYL)ETHYLAMINE	C29H27Br2NO3
3-CHLORO-4-METHYL BENZYLAMINE	C25H24Br2ClNO3
TETRAHYDROFURFURYLAMINE	C22H25Br2NO4
2,4-DICHLOROPHENETHYLAMINE	C25H23Br2Cl2NO3
ETHYL 4-AMINO-1-PIPERIDINECARBOXYLATE	C25H30Br2N2O5
2,6-DIFLUOROBENZYLAMINE	C24H21Br2F2NO3
2-IODOBENZYLAMINE	C24H22Br2INO3
2-METHYLBENZYLAMINE	C25H25Br2NO3
BENZYLAMINE	C24H23Br2NO3
3-METHYLBENZYLAMINE	C25H25Br2NO3
2-METHOXYPHENETHYLAMINE	C26H27Br2NO4
3-METHOXYPHENETHYLAMINE	C26H27Br2NO4
2-ETHOXYBENZYLAMINE	C26H27Br2NO4
(R)-(-)-1-CYCLOHEXYLETHYLAMINE	C25H31Br2NO3
4-METHOXYPHENETHYLAMINE	C26H27Br2NO4
2-FLUOROBENZYLAMINE	C24H22Br2FNO3
2-CHLORO-6-METHYLBENZYLAMINE	C25H24Br2ClNO3
4-CHLOROBENZYLAMINE	C24H22Br2ClNO3
BETA-METHYLPHENETHYLAMINE	C26H27Br2NO3
1,1-DI(P-ANISYL)METHYLAMINE	C32H31Br2NO5
MAYBRIDGE BTB 12133	C27H29Br2NO6
DL-2-AMINO-1-PENTANOL	C22H27Br2NO4
L-PHENYLALANINE P-NITROANILIDE	C32H29Br2N3O6
ETHYL 3-AMINOBUTYRATE	C23H27Br2NO5
(1S,2R)-(+)-2-AMINO-1,2-DIPHENYLETHANOL	C31H29Br2NO4
2-FLUOROPHENETHYLAMINE	C25H24Br2FNO3
2-ETHYLHEXYLAMINE	C25H33Br2NO3
3-FLUOROPHENETHYLAMINE	C25H24Br2FNO3

-NR'R"	Formula
(1S,2S)-(+)-2-AMINO-3-METHOXY-1-PHENYL-1-PROPANOL	C27H29Br2NO5
NONYLAMINE	C26H35Br2NO3
2,5-DICHLOROBENZYLAMINE	C24H21Br2Cl2NO3
2-METHYLCYCLOHEXYLAMINE	C24H29Br2NO3
3-METHYLCYCLOHEXYLAMINE	C24H29Br2NO3
3-N-PROPOXYPROPYLAMINE	C23H29Br2NO4
2,3-DIMETHYLBENZYLAMINE	C26H27Br2NO3
3-CHLOROBENZYLAMINE	C24H22Br2ClNO3
4-TERT-BUTYLCYCLOHEXYLAMINE	C27H35Br2NO3
(1S,2S)-(+)-THIOMICAMINE	C27H29Br2NO5S
2,4-DIMETHYLBENZYLAMINE	C26H27Br2NO3
2-AMINOETHYL PHENYL SULFIDE	C25H25Br2NO3S
PHENETHYLAMINE	C25H25Br2NO3
TYRAMINE	C25H25Br2NO4
L-TYROSINE METHYL ESTER	C27H27Br2NO6
BENZHYDRYLAMINE	C30H27Br2NO3
4-METHOXYBENZYLAMINE	C25H25Br2NO4
2,3-DICHLOROBENZYLAMINE	C24H21Br2Cl2NO3
GLYCINE N-BUTYL ESTER HYDROCHLORIDE	C23H27Br2NO5
D-(-)-ALPHA-PHENYLGLYCINE ETHYL ESTER HYDROCHLORIDE	C27H27Br2NO5
4-CHLORO-2-FLUOROBENZYLAMINE HYDROCHLORIDE	C24H21Br2ClFNO3
TRANS-2-PHENYLCYCLOPROPYLAMINE HYDROCHLORIDE	C26H25Br2NO3
ETHYL 4-AMINOBUTYRATE HYDROCHLORIDE	C23H27Br2NO5
DL-HOMOCYSTEINE THIOLACTONE HYDROCHLORIDE	C21H21Br2NO4S
4-NITROBENZYLAMINE HYDROCHLORIDE	C24H22Br2N2O5
NORPHENYLEPHRINE HYDROCHLORIDE	C25H25Br2NO5
GLYCINE ETHYL ESTER HYDROCHLORIDE	C21H23Br2NO5
DL-ALANINE ETHYL ESTER HYDROCHLORIDE	C22H25Br2NO5
SARCOSINE ETHYL ESTER HYDROCHLORIDE	C22H25Br2NO5
4-NITRO-N-PROPYLBENZYLAMINE HYDROCHLORIDE	C27H28Br2N2O5
PIPERIDINE	C22H25Br2NO3
3-METHYLPIPERIDINE	C23H27Br2NO3
3-(HYDROXYMETHYL)PIPERIDINE	C23H27Br2NO4

-NR'R"	Formula
1,2,3,4-TETRAHYDROISOQUINOLINE	C26H25Br2NO3
2-ETHYLPIPERIDINE	C24H29Br2NO3
3,4-DICHLORO-N-ETHYLBENZYLAMINE	C26H25Br2Cl2NO3
2-METHYLPYRROLIDINE	C22H25Br2NO3
N-ETHYL-N-PROPYLAMINE	C22H27Br2NO3
4-METHYLPIPERIDINE	C23H27Br2NO3
(S)-(+)-2-(METHOXYMETHYL)PYRROLIDINE	C23H27Br2NO4
N-BENZYLETHANOLAMINE	C26H27Br2NO4
DIBENZYLAMINE	C31H29Br2NO3
4-BENZYL-4-HYDROXYPIPERIDINE	C29H31Br2NO4
(R)(-)-2-BENZYLAMINO-1-BUTANOL	C28H31Br2NO4
N-(N-ETHYLAMINOACETYL)-2,6-DIMETHYLANILINE	C29H32Br2N2O4
N-ETHYL-O-METHOXYBENZYLAMINE	C27H29Br2NO4
MAYBRIDGE NRB 01961	C30H33Br2NO5
2-((N-ETHYLAMINO)METHYL)-4-NITROPHENOL	C26H26Br2N2O6
MAYBRIDGE SEW 01484	C31H29Br2NO4S
3-AZABICYCLO[3.2.2]NONANE	C25H29Br2NO3
N-(2-METHOXYETHYL)ETHYLAMINE	C22H27Br2NO4

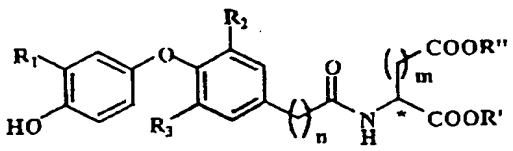
13. The compounds as defined in Claim 1 having the structures





or a pharmaceutically acceptable salt or ester(s) thereof.

14. The compounds as defined in Claim 1 having the structures



wherein R_1=isopropyl, methyl, ethyl, cyclopentyl, cyclohexyl, and R_2 may be independently selected from Br, Cl and Me, n= 0, 1, 2 and 3, m= 0, 1, 2 and 3, * denotes either D or L stereochemistry and R' and R'' are independently selected from hydrogen, lower alkyl, especially ethyl and methyl, and where R' and R'' represent prodrug ester forms known in the art such as pivaloyloxymethyl or dioxolenylmethyl.

15. A method for preventing, inhibiting or treating a disease associated with metabolism dysfunction, or which is dependent on the expression of a T_3 regulated gene, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.

16. The method as defined in Claim 14 wherein the disease associated with metabolism dysfunction or which is dependent on the expression of a T_3 regulated gene is obesity, hypercholesterolemia, atherosclerosis, depression, osteoporosis, hypothyroidism, goiter, thyroid cancer, glaucoma, cardiac arrhythmia, congestive heart failure, or skin disorders.

17. The use of a compound according to Claim 1 in the preparation of a medicament for the treatment of a disease or disorders which is dependent on the expression of a T_3 regulated gene.

18. The use of a compound according to Claim 1 in which the disease or disorder is selected from hypothyroidism, hypercholesterolemia, obesity, skin disorders, glaucoma, cardiovascular disease, congestive heart failure and other endocrine disorders related to thyroid hormone.

19. A pharmaceutical composition comprising an effective amount of a compound according to Claim 1 or a pharmaceutically effective salt thereof, together with a pharmaceutically acceptable carrier.

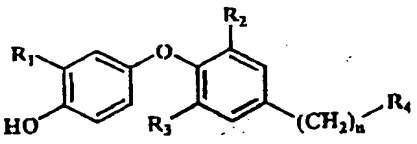
20. The method according to Claim 15 in which the skin disorder or disease is dermal atrophy, post surgical bruising caused by laser resurfacing, keloids, stria, cellulite, roughened skin, actinic skin damage, lichen planus, ichtyosis, acne, psoriasis, Dernier's disease, eczema, atopic dermatitis, chloracne, pityriasis and skin scarring.

21. A method to treat skin disorder or disease by the use of a compound of Claim 1 in combination with a retinoid or a vitamin D analog.

NEW THYROID RECEPTOR LIGANDS

Abstract of the Disclosure

New thyroid receptor ligands are provided which have the general formula



in which:

n is an integer from 0 to 4;

R1 is alkyl of 1 to 6 carbons or cycloalkyl of 3 to 7 carbons;

R2 and R3 are the same or different and are hydrogen, halogen, alkyl of 1 to 4 carbons or cycloalkyl of 3 to 5 carbons, at least one of R2 and R3 being other than hydrogen;

R4 is a heteroaromatic moiety which may be substituted or unsubstituted, an amine (NR'R"), a carboxylic acid amide (CONR'R") or an acylsulphonamide (CONHSO2R') derivative, or a pharmaceutically acceptable salt thereof, and all stereoisomers thereof.

In addition, a method is provided for preventing, inhibiting or treating a disease associated with metabolism dysfunction or which is dependent upon the expression of a T3 regulated gene, wherein a compound as described above is administered in a therapeutically effective amount. Examples of such diseases associated with metabolism dysfunction or are dependent upon the expression of a T3 regulated gene include obesity, hypercholesterolemia, atherosclerosis, cardiac arrhythmias, depression, osteoporosis, hypothyroidism, goiter, thyroid cancer as well as glaucoma, congestive heart failure and skin disorders.

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